Cover Page

I N D E X

Biological Therapeutics for Rare Plasma Protein Disorders

June 14, 2005

I N D E X (Cont'd.)

KEYNOTE: "---" denotes inaudible in the transcript.
"*" denotes word was phonetically spelled.

P R O C E E D I N G S

FDA Introduction: Case Studies

Andrew Chang, PhD, Session Chair

DR. CHANG: Good morning. Welcome to day two of the workshop. Now before we start the first session I would like to remind you that this auditorium, you cannot bring the food and drink in this auditorium. So, please, compliance with this rule, otherwise we will have difficulty to get this auditorium next time. For those of you do not know me, my name is Andrew Chang. I am currently Associate Director at Division of Hematology, Office of Blood and ---. I am going to chair the first session of this morning on the case studies.

(Slide.)

There are two main objectives for this first session. We would like to review current product development experience and also we would like to further identify challenges and opportunities through the case studies. Now this morning we have actually a list of the speakers to cover several products that are either under development or that have already been licensed in the different regions. This includes protein C and coagulation factor XIII, antithrombin

III, platelet disorder, and enzyme to treat Fabry's disease. At the end of this session we will have open panel discussion, and Dr. Keith Hoots will lead that panel discussion.

So without further ado, let me first introduce the first speaker for this session, Dr. David Gelmont from Baxter Health Care, and is the title of his presentation is "Severe Congenital Protein C Deficiency." Welcome.

Severe Congenital Protein C Deficiency

David Gelmont, MD

DR. GELMONT: Thank you. Thank you very much. Good morning to all of you. Protein C, a case in point in the developing of rare blood disease in Europe and in the United States.

(Slide.)

Something is wrong.

(Adjusting equipment.)

Okay. So the definition of severe congenital protein C deficiency is homozygous or double heterozygous. They should have very low protein C level, below 20 percent activity in an asymptomatic state.

(Slide.)

The epidemiology is as you can see. It is a rare disease, one in 160- to 350,000 live births. We identified

today only 17 subjects in the United States who are known to us to have severe congenital deficiency. We don't expect to find more than one to two new cases a year based on our experience, and we have a similar number of subjects in the EU. Most of the subjects die in utero and they don't come to our attention, to any physician's attention beforehand.

(Slide.)

Most subjects present at a very young age, usually neonates and young babies. The babies are born many times with cerebral infarcts and hemorrhage, blindness, infarcted kidneys, and multi-organ disease, dysfunction and failure. Neonates may develop purpura fulminans in the first few hours or days of life, so it is a severe disease affecting very, very young subjects.

(Slide.)

The long-term complications of the disease, many neurological sequelae. Many of them have motor of cognitive dysfunction. Some of them are on dialysis for renal failure. You see a lot of amputation after episodes of purpura fulminans. Many of them are born blind. They need a lot of surgeries and it is a major medical burden on society and healthcare systems.

(Slide.)

Dr. Weinstein asked me why did we develop protein

C. So the major reason for developing protein C was that we have a high level executive at Baxter was a very great champion of protein C, and that is how it was developed. It was developed without essentially a good look at the financial aspects --- ability of this protein, and we went through that and we became committed to this population and to this protein, and that is where we are today. But in the current regulatory and reimbursement climate I don't think that Baxter would be able to develop a protein in the same super-orphan indication as we did with protein C. So I think this is a one-time episode unless the climate will be changed.

(Slide.)

The European approval was granted on July 16th, 2001, by the EMEA, Ceprotin, protein C concentrate, and under exceptional circumstances and, as we talked yesterday, conditional approval. Ceprotin was the first plasma protein to be approved by the centralized procedure.

(Slide.)

This is taken from the European summary basis of approval, and it is the quotation that "The approval was based on the results of efficacy analyses including 12 courses of short-term prophylaxis prior to surgery or invasive therapy and nine courses of long-term prophylaxis."

Then also said, "The benefit of Ceprotin is its anticoagulant effect," and this is the quotation from the EPAR.

(Slide.)

Further on from the European summary basis of approval, "The CHMP, on the basis of quality, efficacy, and safety data submitted, considers that the benefit/risk ratio for Ceprotin is favorable in the approved indication." They also said that, "The marketing authorization was granted under exceptional circumstances because the indications for which the medicinal product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the efficacy of the medicinal product." So that was the basis of the approval.

(Slide.)

But they gave us post-marketing commitments, and there were two major post-marketing commitments. The first one was additional information, and that is why we completed recently a study, prospective study in severe congenital protein C deficiency in this country, in the US. They also asked us to do market surveillance. --- Dr. --- here I will say a word or two about the feasibility of post-marketing surveillance. Those two commitments, post-marketing commitments, were lifted though after -- and we received full

approval after completion of the prospective clinical study and yearly submission for the last four years of the post-marketing surveillance.

(Slide.)

So this is some data from the post-marketing surveillance and in this post-marketing surveillance any drug that left in Baxter warehouses was accompanied by a questionnaire regarding demographics, regarding efficacy and safety of the drug. Now we were able to account for 60 percent of all drug that left Baxter warehouses in Europe; 40 percent we cannot account for, and they probably represent some drug that is still in the pharmacies still not dispensed yet and some drug we cannot account for. So these data essentially represent 60 percent of all drug, and that is year by year. You see almost year-by-year data. You can see in the columns here is the number of patients, very small amount. Nine patients congenital, 44 patients acquired, 79 acquired, 16 congenital, and the last year that we had data here is 47 acquired, 11 congenital. You can see that the consumption of drug is mainly in the congenital. This is how much drug is consumed. About two-something-million units by congenital and only, I don’t know, less than 0.5-million by acquired. So most of the drug went for congenital and very little has been used off label in Europe and a very small

number of subjects were prescribed Protein C.

So in summary, post-marketing surveillance is possible in Europe to give us some data of what is going in market. I am not sure it is feasible in this country, but we did it and we can account for quite a bit of the drug that was dispensed out of our warehouses.

(Slide.)

When we started to design the study for licensure in this country and was also was part of our post-marketing commitments to the EMEA, we faced several things here, several obstacles. We had a small patient population. We were at 18. One died, so it is 17 in the US. Even those subjects who we identified, the occurrence of event is not that common in most subjects.

There was broad range of population age. I mean we had patients who were less than one day old to patients now 27, 28 years old, and it is very, very difficult when you try to have dosing to assess to treatment to get laboratory data. We cannot draw blood from neonates. We are allowed to take one ml to two ml a day, no more than that, while in adults we can take way more blood. So it makes it very, very difficult to run studies in neonates and put them together with adults. It is very, very difficult.

There was no adequate control. I mean, the most,

the best control that we could envision was fresh-frozen plasma, but fresh-frozen plasma to give in the same dose as we give with the concentrate would put the subject in pulmonary edema, hyperprotein anemia, protein --- and a variety of other problems. So you don't have a really good control in this study. The disease severity may inversely correlate with age. If the disease severity is very high the patient dies at a very young age, and only those guys who are also well-treated but less severe enter adulthood and survive to older age.

(Slide.)

So the phase III study was in to demonstrate that protein C concentrate safety and efficacy in the treatment of acute thrombotic episodes, in short-term thromboembolic prophylaxis, and long-term thrombotic prophylaxis.

(Slide.)

We enrolled all known subjects in the US, which were 18, with severe congenital protein C deficiency. Every one that we knew was enrolled. We tried to keep all the 18 in the study. It wasn't that successful. The study design attempted to satisfy and to harmonize both between the EMEA and the FDA requirement, and we attempted to measure both clinical and bio-surrogate markers. We attempted to measure everything because we felt they were such a small patient

population we needed as much details as possible on this population. The historical control data, the study design was we were asked by the FDA to have historical control data, was extremely difficult. Analyzing the literature and trying to get some understanding from the literature what is the natural course and what is the natural course with treatment of these patients was extremely difficult, and I can talk of why it is so difficult later on.

(Slide.)

So what did we learn in the process? Because of the small number of eligible subjects we wanted to include and keep every subject in the study and collect as much data as possible for each episode. That resulted that the protocol developed was cumbersome, complicated and difficult to execute. Now most of you know what it takes to write a protocol, but this protocol was 150, 160 pages, and if you put on top of it the historical control there was another 150 pages. So the total protocol was like 300 pages for 18 subjects. That makes it very, very difficult. The rate of assessment is extremely difficult. That resulted in multiple protocol deviations, and we concluded that we could not conduct a really robust efficacy study in this indication.

(Slide.)

What are suggestions for the approval process?

Well, simplify. One word I would emphasize is simplify the approval process globally, not only here. Simplify clinical trials to consist of PK study and a phase II/III with bio-surrogates. You know, if you look at D-dimer this is a very good marker of the disease. If you don't have D-dimer the patient has no active disease. Sometimes they have D-dimers and you don't see any clinical evidence, but they usually get into trouble when the D-dimers are up. Safety evaluation to be determined maybe by rate of related AEs as a fraction of number of drug administrations or total dose and assessment of the related serious adverse events impact. We such employ only descriptive statistics in a pivotal study analysis. Any other study statistics is going to be very difficult or not useful, and we also suggest to implement better harmonization between the FDA, EMEA, and other ministries of health in obtaining market approval in super-rare or rare indications.

(Slide.)

These are suggestions for post-marketing commitment. We would like to establish a patient registry to collect and publish data regarding the safety and efficacy of drug. Medical monitoring, you know, we have another drug, Aralast, and 86 percent of the patients are being monitored by medical professionals. The other 14 percent of the drug that is being sold is being sold to hospitals, so everybody

that is getting the drug has some kind of medical monitoring. They are not without medical monitoring. Just not sell the drug on the market without the patient being monitored somehow. Post-marketing commitment studies to be evaluated for discontinuation biannually. We don't want an open-ended commitment. It would be easier for all of us to go with this kind of endeavor if we know that there is an end to that. Maybe create and FDA website for super-orphan drugs information for anything regarding the super-orphan drug such as dosing to experiences to safety issues, whatever needs to be done, and how to get information or what key opinion leaders to get advice how to take care of patients. I think that is it. Thank you.

(Applause.)

DR. CHANG: For the interest of time we can take one question.

MR. : You mentioned that the surrogate markers basically was the D-dimer, but you said plural. Were there other surrogate markers?

DR. GELMONT: In the survey? In the phase III study we had -- for example we had --- antithrombin, D-dimer, all the indication of DIC, but the best one was the D-dimer in my opinion. Yes, sir?

MR. : Would you like to estimate how much

the post-marketing surveillance program cost? Either the European one or the US one. What kind of resources did you have to monitor the program? --- sort of figure.

DR. GELMONT: The story in the US is no finished yet. We are in the middle submitting some information to the FDA and we don't know what the post-marketing commitment will be in this country. But with regard to the European, I don't know exactly off hand how much it costs. It is not cheap.

DR. CHANG: We have actually seven speakers for the first session this morning, so it is very important for every speaker to stick to your time, 20 minutes for each presentation. Next presentation will be delivered by Dr. Diane Nugent. She is Director at Division of Hematology, Hemostasis and Thrombosis Research, Children's Hospital of Orange County. Welcome.

Factor XIII: One in Two Million

Finding a Successful Pathway to Product Development for Rare Clotting Disorders

Diane Nugent, MD

DR. NUGENT: Thanks. Good morning. Thank you for including not just me on your speaker list, but our patients, and again I am here to speak for another orphan group of patients, factor XIII deficiency. The focus, although I will briefly mention what the disorder is and the natural course

of disease, but what I would like to stress is what it is like to run a clinical trial for orphan disease. I have had the opportunity to do this with two different, completely different approaches, and that is what I would like to share with you today and maybe talk about future clinical trials for other rare diseases.

(Slide.)

So factor XIII is rare. You heard I believe Dr. Jain quote one in a million, which is encouraging to me because a lot of the literature started out at one in five million, one in three million. So what that means obviously is we are getting better at diagnosing and recognizing the disease. The process of diagnosis is difficult however because the assays, there are really two that are used in the United States. One is the urea solubility, which will only detect rare factor XIII less than one percent, which is the extraordinarily most severe form. There is another --- assay which is run at Asoterics*. We run it in our lab as well, and it will quantitate the amount of factor XIII there, but anything less than 10 percent becomes very unreliable and at 10 percent the range of error is close to five percent activity. It is an activity and therefore dependent on the amount of thrombin that you add.

So the first problem take-home point is here is an

entity that we are challenged by not having as sensitive a surrogate marker as we would like, and so we have incorporated ELISAs to try to make it more sensitive. There are other assays that are being developed actually currently now in Europe, but are not FDA-approved in this country. The natural course of disease is striking for a number of reasons. Obviously it is associated with mucousal and bruising disorders. However, there is an extraordinarily high rate of intracranial hemorrhage, and depending on the center it has been reported as high as 60 percent. This is one of the major presentations of this disorder besides the umbilical stump bleeding and so on which we are all trained in medical school to recognize. That, I don't think in the years I have been doing this assay we have had anyone present with that. Almost all of our patients on these studies presented with intracranial hemorrhage.

Why is it with hemophilia, another very well-known disease, the rate of spontaneous intracranial hemorrhage is actually very low? We think of that as being a very severe form of bleeding. This particular disease you may go for years with just a little bit of bruising or some gum bleeding and then all of a sudden have spontaneous intracranial hemorrhage. It is a part of this rare disease that we do not completely understand and a focus of research in our group.

Other things that may bring patients to diagnosis are recurrent miscarriage and poor wound healing. Surgical bleeding is a major presentation as well. Patients initially do well during the surgery, but then have post-operative bleeding that is quite severe.

(Slide.)

This is the structure of factor XIII. It is basically composed of two subunits and two B subunits, and the B subunits are carriers for the plasma form. All the other forms of this factor XIII that are intracellular are only the two A subunits. The way that we primarily know about factor XIII is that we feel it increases clot stability.

(Slide.)

Once the A subunits are actually cleaved away from the carrier subunits -- and this is a two-fold step. This is another thing that makes the assay difficult. It is first a thrombin cleavage and then a calcium activation step, then you have the active form of the transglutomase. What this enzyme does is it cross-links proteins. That is its main job.

(Slide.)

It has credibility affinity for fibrinogen, and so we really recognize it for that job, but it probably cross-

links a lot of other proteins in our body, and we will talk about those momentarily. It is found in many different cells, monocytes, platelets, placenta.

(Slide.)

Because it increases the tensile strength I have to admit that in my primitive way of thinking when I started working with factor XIII I thought it was, as we are taught, the very last step in the clotting cascade. In fact, it is involved in clot formation as soon as the initiation is complete, and I will show you some thrombolastagrams* that are really quite impressive. It is not just that cross-linking step at the very end. It is cross-linking throughout clot formation.

(Slide.)

Here are two examples of cross-linking, and both of these are fibrin clots that are formed. The only difference between these two, the upper and the lower, is a single polymorphism in the factor XIII molecule. Approximately 25 percent of individuals would make the lower form if you are homozygous for that particular polymorphism. The other form is the normal form. So if you actually have a polymorphism in this area you are at risk for actually thrombosis, and it is part of our thrombophilia panel, so cross-linking is very important. In this mesh it not only is fibrin cross-linked,

fibrinogen which in fact the A subunits are closely tied to, but it cross-links alpha-2 antiplasmin within the clot, another factor that slows down clot breakdown, and probably cross-links a fair number of the adhesion molecules, too.

(Slide.)

So here are just a small, a short list of other proteins that get cross-linked by factor XIII. As I said, the affinity for factor XIII cross-linking or binding to fibrin or fibrinogen is one of the highest affinities that we have in biochemistry. This was characterized by Dean Mossier in Wisconsin. Lower affinity activity, however, is probably critically important, so people who have 10 or 20 percent factor XIII may have miscarriages but may not have bleeding from clot instability. Just a thought for those of you who are interested in research in factor XIII. It also interestingly when you look in cytoplasm will track from the cytoplasm to the nucleus, so it is a carrier protein as well and that is a very interesting part of this disease for us.

(Slide.)

The take-home point on this is there is almost a unique mutation for every patient that has been described in our country, and the other place that work has been done extensively in this area is in Europe and in Israel. There are kindreds that share a mutation, but it is incredibly

diverse, and this is a point for anyone working in rare diseases. If this is a situation where every patient has a different mutation, then the disease, the PK for the drug that you are giving, the natural course of the disease may be completely different. So even though you have a rare disease, not all patients with that rare disease are the same, and it is really important to incorporate that thinking into your clinical trials and try to do the molecular characterization which we are trying to do in our lab in factor XIII, and I know people with protein C deficiency, alpha-1 antitrypsin and others are doing that.

(Slide.)

So one of the ways that we look very grossly and in some ways as an acute surrogate marker for us is the thromboelastogram which shows us the time to clot formation, the rate of clot formation and strength, and also how long it takes for the clot to break down.

(Slide.)

Fortunately with factor XIII -- and this is a normal thromboelastogram. This straight line here, the time going from initiation to when this curve starts is what we call the time to clot initiation. Then this shoulder and the angles that are included in this curve tell you about the rate of clot formation over time. The arch, the distance

here, defines the size of the clot, and also you can calculate the strength of the clot in ---. Over time then the clot starts eventually to break down. This is the size of the clot after 30 minutes. This is the size of the clot after 60 minutes.

(Slide.)

This is a factor XIII deficient patient. You note that the initiation time is not affected, which makes sense. However, look at the repetitive with which the clot is formed. The shoulder is much less steep, and in addition the maximal size of this clot is markedly less than normal. The strength of the clot, imagine without having the cross-linking that you saw in that previous slide, the strength is markedly affected. So here it is already at 30 minutes. We are starting to see from here to here significant breakdown, and here we are at 60 minutes. So it does break down more rapidly.

(Slide.)

This is that same patient following a treatment with factor XIII. You notice that factor XIII plays a role in the clot formation, the size, and the strength of the clot, and in addition at 30 minutes protects that clot from breaking down. So this has been a very useful surrogate marker for us. We do the assays as well, the berichrom assay

and the ELISAs, so we try to have a number of markers that we can follow. Doing the assay itself is not perfect.

(Slide.)

Alternatives for therapy are fresh-frozen plasma and of course there is risk of infection. You have to be admitted. This runs in over a period of at least two hours for most patients who get about 20 ccs per kilo. Some go up to four hours. It is protein. Patients don't go into fluid overload, but they do very quickly get sensitized to other plasma proteins. The same is true for cryoprecipitate, which is another alternative therapy for these patients, but because it is a blood product, because we are looking at risks of sensitization, the patients are infused blood in the clinic or in the hospital. So having a product which is heat treated and which can easily be given in the clinic was a big boon and it has also greatly reduced exposure to foreign proteins.

(Slide.)

People that have had intracranial hemorrhage are recommended to receive some form of treatment at least once a month, every four weeks, and in general it is associated with once you stop that process there is recurrent intracranial hemorrhage. So we tend to go on as long as we can with treatment; however, lifelong prophylaxis does result in

hepatitis, and many of the patients in our study, especially the older ones, were positive for hepatitis C.

(Slide.)

So if you leave with nothing more, I want to bring up a couple of points about ways of doing a study for rare disease. The first way is the Fibrogammin P way. That little (3) stands for the fact that in the time that we were actively doing this study starting from about 1998 and really opening it to patients in the year 2000 to the present there have been three changes in company. It started out with Centeon, it then went to Aventis, and now the last few months it has been ZLB. So doing a study on rare diseases where there are alternate products available is a challenge. I want to credit all three of those companies because they supported this project throughout, and even though I think for a while no one was sure that they wanted to proceed with this product clinically.

It is a plasma-derived product, and again this has all four units in it for plasma-derived. It has been used and is approved and has been used safely and very effectively for a long time in Europe and in Canada and Japan. So this is one of those drugs that has approval elsewhere. Plasma-derived I mentioned, intact molecule.

We currently have 60 patients enrolled in 50

centers. Every one of those centers has a separate IRB, and the process of IRB approval was the most challenging part of this study. We are responsible for the distribution of the product and making sure that all the products sent in the SAEs/AEs are reported to our center. Any questions, we are the ones that do all the materials, everything else. Currently this accounts for 18,000 patient exposure days per year with this number of patients.

The cost for the company is the factor is provided for patients without any cost, but there is a cost to the company to maintain this distribution. We have a CRA, a coordinator, and IRB. The company doesn't pay for all of those people, but it pays for a portion of their time. We have over 50 clinical trials at our center just in hematology alone, but this is the most time-consuming study that we have.

(Slide.)

The other project that we have is recombinant factor XIII. It is a new product. We did the initially phase I trial for PK and safety with 11 patients. In this setting it was a recombinant product produced in yeast. Having learned from the Fibrogammin project we decided that we would bring all of the patients to our center, so we had one IRB. The cost was in travel and expense, and during

that time the patients were flown in from all over the United States. Each patient had about five days at a center representing two separate trips, one at the beginning of the month and one at the end, and they were in the hospital actually for 72 hours. The cost of course was for the samples and staff.

(Slide.)

This is the team that I work with, and I want to give them all of the credit for all of the work that gets done, particularly those of you who work or participate in the study and many of you are here. Cathy B. is the person in the center. She is really the pivotal person who gets all that done. The rest of us are nurses, technicians and physicians.

(Slide.)

So the history. Jonathan Goldsmith, where are you? Hey, my mentor, my friend, right, comes to me and says, I have this little project I think you would like to pick up." At that time, yeah, you were my role model and I trusted you, Jonathan.

(Laughter.)

Little did I know. So basically he asked us to reinstitute it. It had been started actually and there were a number of centers participating in I think maybe in 1994;

but somehow it hadn't all quite come together, and I learned why it hadn't come together once I started doing it. So we picked it up, and as I said three companies have been involved.

We called a meeting with potential investigators, mainly those who had been involved in the previous study which had not had IRB approval and safety samples being sent in on a regular rate. Jonathan congealed all that, got all that to work, and the idea was that this was a way as someone had mentioned in their slides yesterday, a way to get the product out to the centers in a compassionate use format. I think it was the European group that says, but there is sort of no compassionate use now. There is only IRB-approved distribution and then there is -- we did one PK right in the beginning of this study, and then the rest of the time collected data on safety, viral studies, as well as inhibitor studies. We went ahead and did an abstract out of the old plasmas; then we entered the first patient on the current protocol. As I mentioned, we are up to 60 now.

(Slide.)

We had to have congenital factor XIII deficiency. These slides were in your handout. Everybody had to come through IRB approval.

(Slide.)

Baseline testing was performed. We did circulating half-life and inhibitor levels throughout the study.

(Slide.)

This is a really important slide that I added last night based on our discussions yesterday. I learned from Mark Skinner you can still add slides right to the very last second. We when we started the Fibrogammin the costs that we assessed and submitted to the company for doing the study was the centers there was no IRB costs in any of the centers that we initially started out with. The factor was administered in the clinic visit. There would have been a clinic visit anyway, so physicians didn't charge for that, nor did the hospitals ask to charge for it. Factor was provided. We did promise each center $1,000 per patient, an amount at the time we thought was huge for when you had a completed patient at 12 months, and then from there on in they could do a monthly infusion and just send us an inhibitor assay with the subsequent years.

Currently -- and this is so important. I think it is one the big hurdles that we have with getting studies done. Currently hospitals, institutions, universities, everybody sees a pharmaceutical company's name associated with a study and they say, "That's it." You know, "We are charging up to the nines." So there is one center that

contacted me this week actually that said that besides now the $2,000 IRB cost -- which most centers have, including mine -- there is full charge to the company for the office visit, for the overhead to that visit which is close to $200 or $300 per office visit, the cost of the nurse, pharmacy charges and so on, and that is taking at that one center alone from $6,000 up $60,000 in one year. That center is one of our largest centers. They have between five and seven patients. That does not include the cost of factor. I pointed out that in real dollars if they were paying for the factor it would be $240,000 alone just for the factor at that center. But if you figure we have 50 centers, this is one of our larger ones, but at 50 centers let's say it is 10,000 per center for those kind of overhead. It would be $500,000 per year, so the cost of running a clinical trial in this way has really gone up. So between the factor and the cost per patient and then over the years, as I said this is our fifth year, it is getting very expensive.

(Slide.)

I will skip through our responsibilities.

(Slide.)

I mentioned that we had a lot of distribution issues which would take a lot of time, but happened. We shipped quarterly and so. The SAEs are very unremarkable.

Headaches are a recurrent theme for whatever product you give factor XIII. There were two deaths, both unrelated, one suicide and one auto accident. The study is still open, and we added on two more patients this year.

(Slide.)

We have an excellent response to therapy. We don't have any inhibitors. We don't have any reactions to this. There is much less allergic reactions. It is something that can be given in clinic or even at home. I really encourage the point that someone made about having a research team or team go out and give factor to the home with rare disease. Some of these patients live over 500 miles away from their center, and it is not really easy for them to come on a monthly basis.

(Slide.)

The other product that we did, just in the last five minutes, is recombinant XIII, and basically it is only the two A subunits. So the key point here is that you are dependent on your own endogenous B subunits to bind to these proteins and carry it where it needs to be. Therefore, this product does not work for factor XIII deficiency that is present on the basis of B subunit deficiency. This happens to be the minority of patients with factor XIII deficiency, have B subunit deficiency, but it is pretty clear that you

will see we did have one out of the 12 patients. We had one had a B subunit. So we added one other patient at the end just to get normal PK.

(Slide.)

This was a single-center study. As I said, we brought all the patients to one center. We did the IRB. This study was done, completed, within four-and-a-half months.

(Slide.)

It is a much more efficient way to do it, and I would say given the time and accumulation the other way probably more cost effective.

(Slide.)

We did the dose finding as well as the PK. We had a good distribution. This is we added the one patient at 50 unit per kilo because we discovered that we had a B subunit deficient patient.

(Slide.)

Day seven and 14 we had mobile units go out and collect blood from those patients where we needed the day seven and 14. It did not make sense to fly them back. These are certified agencies that go out to do this, and I think this an area of support, financial support, that we really need.

(Slide.)

You can see there was a lot of data collected in the first 72 hours.

(Slide.)

Then the most common adverse effect was headache.

(Slide.)

We found that the half-life was similar to that found in plasma which is 8.5 days. The median dose response was 2.4 percent increase in activity per unit of factor XIII, and we did see significant changes on the thromboelastigram.

(Slide.)

I included this slide just to point out that whereas the T1 half in hours was very, very good no matter what the dosage range was. Here is the half-life for our B subunit depletion patient, which is only nine hours. So you could use it quickly, but don’t expect it to stay around like the other ones do.

(Slide.)

I am going skip this and just go to the conclusions to stay on track.

(Slide.)

So recombinant actually does appear to be safe and effective. It is not good for B subunit deficient patients. We have only done the phase I, so a much larger study needs

to done.

(Slide.)

Surrogate markers are, as I said, not the best for this, but it is important that nobody had any kind of bleeding whatsoever on this.

(Slide.)

Basically there are two things that I think are really important to talk about on current issues, and this is something where this is one of those rare disease where we can't have a placebo. If you have someone who has had intracranial hemorrhage you really cannot have an arm where they are getting placebo. It is unethical. The second thing is that if you don't present with intracranial hemorrhage, if you have one of the other forms of factor XIII presentation, the milder forms, that disease is not comparable to the one that where we have intracranial hemorrhage on the spontaneous basis. There is I think a lot of reasons to have these studies done with rare patients in one center, get everybody in. There is much more consistent lab data collection as far as the company is concerned. The IRB issues are minimized, and I think one thing that we could do to harmonize clinical trials is to perhaps draft a statement from our group today asking universities and hospitals to recognize that the cost of doing clinical trials for rare diseases should if we are

going to be doing them in a million different sites and you are only going to be having one patient per site that there should be some cost recognition to that, and perhaps even have GCRCs if available to do that. But it is certainly going to be a challenge if all of the institutions require so much money for each of those patients. I will stop there.

(Applause.)

DR. CHANG: Well, we make all the presentation slides presented at this workshop available on the website. Now we are open for questions.

MS. : I was wondering what type of inhibitor assay you used in your recombinant product. I mean, the type of the product is completely different if the normal --- assay you think is going to be suitable assay for --

DR. NUGENT: Oh, I am sorry. I didn't see where you were. Sorry.

MS. : I was wondering the type of inhibitor assay you used in your recombinant type of product.

DR. NUGENT: There really is only two ways to look for inhibitor. One is through an activity and one is to see through competitive inhibition with a radio-labeled assay to see if you get decreased binding of factor, and then, finally, we also screen for human immunoglobulin within our ELISA. So in other words if there is antibody IGG or IGM

attached to the factor XIII -- we have a normal factor XIII. There is actually the reason this is so long is we looked in about five different ways; activity, through ELISA, and through competitive inhibition.

MS. : How frequently you were looking for inhibitor ---?

DR. NUGENT: In the literature there have only been three instances of inhibitor factor XIII. It is exceedingly uncommon.

MS. : I mean in your study.

DR. NUGENT: In our group? There was none. There was none.

MS. : How frequently were you looking for them?

DR. NUGENT: In the Fibrogammin assay we looked about -- let’s see. We looked four times in the first year and we have looked annually ever since. We get an annual sample. So for each of those days of exposure for Fibrogammin we can calculate per exposure day the incidence of inhibitor, and we haven’t had any yet -- thankfully. The recombinant was just a phase I, so they were only exposed over those 30 days. We did look though again.

DR. CHANG: Jerry.

DR. HOLMBERG: I know I am from the government and

acronyms are supposed to be very familiar to us, but what is GCRC?

DR. NUGENT: GCRC is general clinical research center. It is some institutions have funding set aside. Our floor has or our hospital has few rooms which are dedicated rooms for clinical trials. We can get them at a different rate that a full hospital room. It is underwritten by the hospital. Many institutions and universities have grants from the federal government, GCRC grants for this.

DR. CHANG: We will have opportunity to ask more questions at a panel discussion. Let me take two more questions. Amy.

DR. SHAPIRO: Thank you, Diane. For these rare diseases, you know, one of the things we grapple with is the issue of defining efficacy when really what we are doing is sometimes we are defining treatment for disease, for rare disease, because it is unknown. I am starting to wonder if efficacy for some of these rare diseases for these proteins is just simply levels. That you give this product, that you have this half-life, you get these levels and inhibitor development in a sense. The rest of it is really defining what the needs are for the natural course of the disease and treatment for certain episodes, which is different than efficacy.

DR. NUGENT: Well, in a way we shot ourselves in the foot with Fibrogammin because what we realize now is that many patients actually have a much longer half-life. About half of the patients the half-life is actually much longer, and there are some patients that never fall below 20 or 30 percent, and so they never bleed. So when we are looking for some evidence that we are being efficacious as far as an actual bleeding episode it never happens. So, you know, thank God for noncompliance. If we didn't have patients that weren't compliant we wouldn't see that actually patients do bleed when they are off of the protocol. But because of the ethics of stopping it for our patients, we -- you know, choosing that four-week time we guarantee that they are not going to break through if they are compliant. But out of those patients there have been five who have been noncompliant who have had bleeding episodes, and in addition there are patients that give us a history -- we give a questionnaire each, you know, month that is part of the study -- that do describe bruising at the end, you know, so -- but that is all we can do.

DR. SHAPIRO: But those are symptoms related to levels essentially.

DR. NUGENT: Right.

DR. SHAPIRO: Which is defining --

DR. NUGENT: The symptoms are better than the assay.

DR. SHAPIRO: Yes, but it is defining the disease in a sense.

DR. NUGENT: Exactly right.

DR. SHAPIRO: So could we simplify these protocols by looking at very simple safety and efficacy?

DR. NUGENT: We have tried to put all of that into these. So the questionnaire, the bleeding questionnaire on bruising and so on, we have included that and we are hoping that that along with whatever else we have as far as surrogate markers will work. But, you know, where you have no assay at all that is all you can do.

DR. CHANG: Okay. The next speaker is Dr. Françoise Rossi. I hope I am pronouncing your name right, and the presentation she is going to give is opportunities for patients with rare diseases to access therapeutic proteins.

Opportunities for Patients with Rare Diseases to Access Therapeutic Proteins

Françoise Rossi, MD

DR. ROSSI: I am grateful to be able to present the role of LFB in making available several plasma therapeutic proteins and to show how this could be an opportunity for

patients with rare disease to access these products in the US.

(Slide.)

In a few words, LFB is a state-owned company created by law in 1993, the law which reformed the blood transfusion system in France and established actually the French agency for evaluation of medicine and product. LFB is the first nonprofit fractionator worldwide.

(Slide.)

It ranks sixth among laboratories supplying hospitals in France with providing 19 medicinal products for around 500,000 patients treated annual in the management of 80 pathologies, and some of which are very rare diseases.

(Slide.)

Here is the portfolio of LFB with three ranges or products, immunology, hemostasis, and intensive care. It is quite a big portfolio for a plasma-derived product company knowing that the economical balance is achieved once there is the production of four products.

(Slide.)

Among those 19 products, 14 are dedicated to rare diseases. Hepatitis B immunoglobulins for transplanted patients, IVIG in some indications, the whole range of hemostasis from the product of LFB, factor IX, factor VIII,

factor VII, highly-purified von Willebrand factor, factor XI, and a combination of von Willebrand factor and factor VIII. In the intensive care there is antithrombin, fibrinogen, prothrombin complex, alpha-1 antitrypsin, and finally C protein.

(Slide.)

Here is the epidemiology, and I am not going to be long on that slide, showing that it ranged from one to a few millions to one to 500,000 inhabitants.

(Slide.)

But on this table I try to estimate the number of patients that could be potentially treated in the US with LFB products. This estimate is based on the number of patients that are actually known to be treated in France with our products and based on the ratio between the French population and the US population of one to five. So here are the number of the patients and validated kind of the estimate by --- the estimation of hemophilia A, B, and the von Willebrand disease patients with the citizen numbers, and the are roughly quite similar. Maybe a little less for hemophilia, but those are numbers from ‘98. So on the whole there are 10 to 500 patients depending on the deficiency to be treated in the US.

(Slide.)

According to the FDA definition a rare disease

affects less than 200,000 persons in the US, and the figures for hemophilia A, B, and von Willebrand disease are well within this definition. Whereas for LFB products the number 10 to 500 is actually somewhere between 1,000 to 10,000 less than the FDA definition, so that is -- I call them hyper-orphan, but we all agree that they have to be dealt with in a very specific manner because of the epidemiology. But it is not because there are only a few patients to be treated that in this --- process and development should be any different from any other plasma-derived product.

(Slide.)

There are constraints. There are technical constraints, those plasma-derived products derived from a subfraction of full plasma pool.

(Slide.)

Here on this fractionation tree for most of the products of LFB you can see that starting with a common plasma pool, a full-sized batch plasma pool, are derived several plasma proteins with their own process. But it is not possible to make a sub-pool to start with to get to a small batch size product for a small population.

(Slide.)

Often these products and this process have a very low yield. So to make these products is a complex succession

of purification steps inducing a high impact of consumables in the manufacturing cost, and here I am going to show you the flowchart of the fractionation process of alpha-1 antitrypsin at LFB.

(Slide.)

So they are complex products, and therefore they call for a complex regulation as well by European and national authorities including plant authorization, inspections, European GMPs including specific GMPs for blood products and authority controlling the batches with the cost involved, and important sample library, sometimes 30 years for some of them. Although this leads actually to a very low minor return on investment. That is enough to complain.

(Slide.)

Now I would like to open a window on the French registration system, because I think it can bring more to what was presented, especially in comparison to the European system, because one can find similar mechanisms to register product when the full demonstration of benefit and safety is not yet acquired. So as anywhere else, a regular marketing authorization and a name patient basis. There is a specific mechanism of a cohort temporary authorization for use, ATU, that is dedicated to products that do not have yet a full marketing authorization.

(Slide.)

And this is a full regulatory status, and you can find here that is the website of ---, the French agency.

(Slide.)

The aim is to provide access to some promising medicinal products where there is a public health need including rare diseases in the absence of any suitable therapeutic alternative and when there is a benefit that is presumed. That means that at the time again a full demonstration is not yet acquired, but there is a presumption for it. To be granted ATU status requires the application and dossier, and this dossier has to include a protocol for therapeutic use that is going to collect all the information about the use of the product.

(Slide.)

Here is the list of the requirements, short list of the requirements that has to be described in the protocol during the application; and you see that all the dispensing conditions, the monitoring of patients, have to be planned in the protocol, and the information that is to be collected includes characteristics of patients treated, effective use of the medicinal product, and all the pharmaco-vigilance. So this is protocol forcing an active gathering of data during the use of the product and all the safety events during the

use of the product in routine and not -- and also in all patients treated. That is mandatory that whenever a patient is treated under the ATU status all patients have to be followed in this protocol. So this is also a mandatory pharmaco-vigilance, active pharmaco-vigilance that might answer the question we had yesterday.

(Slide.)

There is also obligation for periodic reports which include all the information about the use and the pharmaco-vigilance.

(Slide.)

So what level of data can we expect to be able to collect and could be required for registration of hyper-orphan products? I would base my proposal on the experience of LFB. These products, for most of them, are already fully registered on the French market. Some of them are used on a name basis in other countries, and just I would like to recall that these products were actually on the market available in France before plasma-derived stable product fell under the pharmaceutical regulation and became a medicinal product. That was the law in ‘93 and the product had to be registered in ‘95. So there is a history of this product before marketing registration, which means that in a way it is a model for the US to be able to benefit from data

collected for use of a product before registration.

(Slide.)

I forgot to mention that there is a mistake in this slide. This is not a reduced -- no, that is fine. On your paper, yes. On your paper you have reduced pharmaceutical quality. This is a full, high-level pharmaceutical quality.

(Slide.)

And all these products have a high purity and very satisfactory viral safety status.

(Slide.)

So the non-clinical documentation is rather common. It is a little bit lighter than for general products, but this is a common feature of biological products and plasma-derived products, and anyway it is based on ICHS6. Specification can be made for pharmacology depending on the product as well as the pharmaco-dynamic animal models.

(Slide.)

Clinical documentation. Here is a hierarchy of strengths of evidence ranking from N-of-1 randomized trial to case report, and all of these levels of proof bring information, and non of them can be neglected. For substantive therapy, which is the case for most of these plasma therapeutic proteins, the regular approach, the conventional approach has to be -- I mean cannot be followed

as we have seen in the previous presentation this morning already. So it is important to take into consideration any level of evidence. Of course with the weight that it has to have in the hierarchy.

(Slide.)

I would like to add to this table retrospective studies, because they can be informative as prospective studies when they are well-managed and especially when a great deal of attention is brought to exhaustiveness and -- and I don’t know. There is another factor that comes into the strength of the retrospective study. I am sorry, I just -- it escapes me.

(Slide.)

So what are the clinical data that LFB was able to collect and that it is possible to collect for these products?

(Slide.)

I will start with fibrinogen. There are only two products available to my knowledge. Clottagen, which is the LFB product which is in France under the ATU status, and Haemocompletan, which is a ZLB product present in France under exceptional importation to cover the public health need. They are rather old products and as we heard yesterday ZLB is developing a new fibrinogen that will be produced with

a much higher --- that will be able to cover the needs and with the improved virological safety.

(Slide.)

LFB --- for fibrinogen pharmacokinetic study in three afibrinogenemic patients, and a retrospective efficacy and safety study in 15 patients documenting 16 surgery and seven bleeding episodes. Those figures of course can seem quite low. However, 15 patients have been entered into the retrospective study, and 15 is half the number of known treated patients in France. So you can imagine what kind of study that would be if this ratio would be taken into account for regular frequency disease. Along with those performed studies there is documentation on the published experience and there is also the protocol for therapeutic use. The published experience as well as the registries we talked a little bit about yesterday and historical control today can add a lot of information and support the evidence of the benefit of the product and benefits/risk balance of the product.

(Slide.)

Factor XI, Hemoleven, you probably know this product by the literature or reported cases of disseminated intravascular coagulation. However, I would like to bring to your attention other data. The product was for a time under

an ATU status, therefore it had a protocol --- and a follow-up, and a one-year ATU follow-up allowed to follow 12 patients during 28 infusions and allowed the evidence of a high benefit to the patients and a positive, very favorable benefit/risk ratio with any DIC reported in this active follow-up of patients. Along with this follow-up there was a published experience documenting PK and efficacy and safety data in 35 patients with 100 infusions. So what I would like to stress is that the benefit ratio of a product has to be considered in the context of proper use, and that was the case almost always during the 12 years of life of Hemoleven, which is still alive.

(Slide.)

Here is a slide condensing the information that were collected for other hyper-orphan products of LFB. Alpha-1 antitrypsin, antithrombin, factor VII, --- complex, and C protein. C protein is going to be shown a little bit more in detail this afternoon by Zére Tellier. So you can see that for most of the product a prospective PK study has been performed, including four to nine patients depending on the epidemiology of the disease, and PK study is actually quite important in those substantive therapies so they cannot be neglected. Then there are efficacy and safety studies, either prospective or retrospective, including nine or 10 to

20 patients. Along with the studies, published experiences has always been added. This is fading if there is another we have for the next speaker. Published experience, always very important, and actually one of the products has been, this one, has been registered under Article 10.1.a of the European Commission directive. That is a full -- the whole file is a bibliographic documentation. So that tells us how informative can be also the published experience with that product or other similar products.

(Slide.)

So to wrap up, this kind of data that have been collected and can be collected for pre-licensure level of evidence, pharmaco-kinetic, efficacy study either prospective but always adapted to the epidemiology, and we saw that in previous talks and probably in the next ones, as well as retrospective studies. Most of the time it is actually possible to get clinical endpoints because the time frame of the benefits, the effect of the product is relatively short for some of the products, but these clinical endpoints no doubt ad strength to the retrospective study. Published experience and post-licensure data collection which will add to the benefits/risk assessment.

(Slide.)

Let’s turn now to the follow-ups of the patients

since this is, as we discussed yesterday quite a bit, is an important issue. I see it as being done in three possibilities. An ATU-like follow-up, that means a prospective follow-up that is mandatory in all patients; a promoter post-marketing surveillance, all the regular pharmaco-vigilance, so the current-like follow-up.

(Slide.)

Here again the protocol has to be submitted when the application -- at the time of the application of the product, and plans for collections of all data, efficacy and safety data with mandatory active pharmaco-vigilance and reported yearly. LFB is performing a post-marketing surveillance for its coagulation factors, and that is to be extended to factor XI and fibrinogen.

(Slide.)

This post-marketing surveillance is going to follow all treated patients in participating centers up to three years, and documents not only the safety of the products, but also the efficacy. So it is a way to collect data, and its aim is to insure consistency between the data collected during the clinical trials on selected patients and routine use on the general population.

(Slide.)

Finally, the regular pharmaco-vigilance. There is

a system in France as in Europe of periodic safety update reports that are timely, and they can be very informative at least in terms of alert if notification is highly enough in an --- way.

(Slide.)

Actually the French pharmaco-vigilance system is known to be quite efficient, and I borrowed this table showing that 42 percent of the reports of factor VIII inhibitor among all the countries listed here come from France, which highlights the efficiency of the pharmaco-vigilance system and not the sensitivity of patients to inhibitor.

(Slide.)

So in conclusion, the FDA requirements for blood products, the collection centers, the plasma collection centers, have to be FDA approved as well as the plants, the workshops, the utilities, the documentation, and so on. The product can be brought available to the patients through an IND after consultation with FDA and performed in the US, and there is a full registration file with all the documentation and probably more that I am not aware of.

(Slide.)

In here I would like to give suggestions for non-US hyper-orphan products to be available in the US. There is no

negotiation on the plasma origin and approval by FDA. However, there is a need, and that has been mentioned quite a bit already, for mutual recognition, at least for the European GMP standards, the inspections, the authorization of plants and so on. The process should be fully described and actually the full pharmaceutical file has to be approved by FDA or mutually recognized if --- has been granted by a European authority.

The thing is that those products as earlier mentioned do not have a European authorization except for C protein because they have national authorization and cannot go as orphan on mutual recognition, but sometimes they are on mutual recognition and present on several European member states. So I understand that harmonization of the assessment of files is a little bit more difficult than inspection standards and authorizations.

Then if a non-US product is going to be used in the US there is a need for a pharmaceutical structure able to carry out the logistics and also to ensure a very high level of traceability, which is a very important thing. Finally, there is a need for adapted pricing policy that will address the complexity of the process but also the limitation of the plasma valuation in case of US plasma.

(Slide.)

On the clinical side, the efficacy and safety study of data gathered and to be assessed should be looked at with the allowing of several levels of evidence and for new -- that is for product already on the market somewhere else other than the US; and for new products of course prospective study will be required, but always powered according to the epidemiology of the disease.

Now the follow-up of the patients would bring reassurance on the safety either through protocol for therapeutic use or for prospective post-marketing surveillance protocol, and that would be able to collect data on the benefit and safety surveillance allowing to improve the fullness of the benefit/risk ratio of the product. That is the regulatory package that seems reasonable for non-US hyper-orphan product to be made available to US patients. Thank you very much.

(Applause.)

MR. : A quick question. How --- efficient in your ability to gather data? What is the mechanism that you have that allows you for example ---? Is this a state-run ---? (Mic not turned on.)

DR. ROSSI: Yes. The system in France, the pharmaco-vigilance system in France is mandatory. There is a special decree for plasma-derived pharmaco-vigilance with

coordinators in various hospitals, so there is an obligation to notify. Of course there is always --- notification like everywhere. That is the weak point of spontaneous pharmaco-vigilance, but it happens the structure, the system in France, is quite efficient.

DR. CHANG: Donna.

DR. DiMICHELE: Thank you, Françoise. I have a few questions. The first is in the ATU system that you are using prior to full medicinal approval -- is that what it is called, medicinal approval? How many products -- have all the products made it through the ATU process to medicinal approval? What is the time frame given the structure of the ATU process for getting these products from ATU status to medicinal approval?

DR. ROSSI: It is a little bit difficult. Also you have to remember that the products, all of these products, were present on the market before this registration obligation, and they were made by various fractionation centers in France and they were -- the centers were gathered as one pharmaceutical company, LFB, and it took a time to put up registration files. So for some of them, the first ATUs, cohort ATUs, were dedicated for those products, and that was a way. The status in the decrees existed. That was not a new mechanism, but the first granting of the ATU were given

for those products. Usually the ATU is really dedicated to providing products before the marketing authorization, and there is some kind of an obligation to reach the marketing authorization. For LFB's products some were right away granted marketing authorization and some other an ATU. The ATU is renewed yearly. It should not last very long.

DR. DiMICHELE: But it does take several years. The process takes several years.

DR. ROSSI: It could take several years, yes.

DR. DiMICHELE: And the other quick questions. In the post-marketing surveillance structure that you have, is that voluntary or is that obligatory for all the patients that continue on the product?

DR. ROSSI: If it is under ATU it is mandatory for all the patients, and actually Fibrogammin was under or is still maybe under an ATU and has this follow-up mandatory also.

DR. DiMICHELE: But once you get the approval, the full approval, marketing approval, the post-marketing surveillance that you described?

DR. ROSSI: Is not any longer needed because you have gathered enough data to fulfill the full evaluation of the product.

DR. DiMICHELE: And has there ever been an efficacy

or a safety data that has not been captured in this method?

DR. ROSSI: Has there --?

DR. DiMICHELE: Has there ever been a safety or efficacy issue with any particular product that has not been captured by this process that you have gone through?

DR. ROSSI: If it has not been captured then nobody knows it exists.

(Laughter.)

DR. DiMICHELE: No, no, but that has come out later, you know, in general use of the product.

DR. ROSSI: No, no. Not in our experience. No.

DR. CHANG: Jim.

MR. : Thank you, Françoise, for this illuminating discussion. It seems, you know, yesterday we heard a lot about cost projections and how for private industry it is infeasible to make, you know, so many of these rare products, and it seems clear that having a publicly-owned company in the public interest promotes this. But I am just curious whether despite that framework you have looked at the actual cost, the cost of production per unit or the cost of production per patient, as a reality test for the projections are from the private sector.

DR. ROSSI: I don't think we have done such an evaluation on per patients, but maybe Pierre --- has an

answer for that. He can help.

MR. : I am not sure to have exactly understood the question. Can you just reformulate it in order to answer you correctly?

MR. : Yes. The basic question is do you know the cost of production of each of these factors for a rare patient use.

MR. : Okay. As you have seen, the manufacturing process of all the products all together from the very first liter of plasma is spread over a very large number of products and of course you have a couple of pathways where the products are manufactured depending on which products has to be produced. So there are a lot of pathways, and at the end of the day you have cost per product of course, allowing dispatch of the plasma cost, depending on how many products you have manufactured. With this hyper-orphan product it could vary a lot, and of course depending on the yield, on the batch ---, the sample library and so forth. So there is a production cost per unit of product, not per patient, and to be honest there could be also some variations on this price because the process of these products is quite complex and of course as it is fully validated --- speaking you have a couple of batches that are not released for variation in the specifications. So

basically the cost of these products added to what Françoise has presented are additionally impacted by the number of batches that should be manufactured to get enough product released out of the pharmaceutical file; and of course you manufacturer one or two or three batches per year, so you don't master the process like a ---. So all together it is quite valuable. We have of course some evaluation of that, but if the plasma origin has to be changed or whatsoever there are a lot of parameters that could make the cost vary depending on the plasma material, starting material, and so forth. So it is not that easy, not certainly per patient, and even though per unit depending on the yearly data.

DR. CHANG: Let's take a last question. We are a little bit behind schedule.

MR. : I realize this is a minute component of your presentation, but you listed a prevalence in the French population of alpha-1 of 1.5 per million and the rest of Europe has a projected prevalence of about one in 1,000 to one in 2,500, and I wondered if you thought this represents unique genetics in the French population or inadequate detection.

DR. ROSSI: The epidemiology I presented came from Manucci, et al and also from our marketing department, but I cannot tell you specifically. I don't think it has to do

with the French population.

DR. CHANG: Thank you.

DR. ROSSI: Thank you.

DR. CHANG: Next speaker will be Dr. Lisa Payne Rojkjaer, and she is Director, Clinical Development, Hemostasis, from Novo Nordisk. Her presentation title is "Towards the Optimization of Therapy for Individuals with Rare Bleeding Disorders: Case Studies of a Coagulation Factor Deficiency and Congenital Platelet Disorder."

Towards the Optimization of Therapy for Individuals With Rare Bleeding Disorders: Case Studies of a Coagulation Factor Deficiency and Congenital Platelet Disorder

Lisa Payne Rojkjaer, MD

DR. ROJKJAER: Thank you, Dr. Chang, and good morning.

(Adjusting equipment.)

Okay. Great. All right. So the goal of my presentation this morning will be to really discuss the challenges of developing a product for a rare bleeding disorder and specifically with the recent Nova Nordisk experience with two conditions in which Nova VII, which is recombinant human activated coagulation factor VII, was approved for use in Europe.

(Slide.)

These two conditions are Glanzmann's thrombasthenia, which is an --- recessive congenital platelet disorder, and congenital factor VII deficiency, which is arguably the most common of the rare bleeding disorders.

(Slide.)

So to begin with, Glanzmann's thrombasthenia has an incidence of one per million. It is caused by the absence of a functional platelet receptor, which results in defective platelet aggregation and platelet plug formation at the site of vascular injury. It is characterized clinical by mucosal bleeding, mostly commonly by nosebleeds, gum bleeding, or intestinal bleeding, easy bruising, menorrhagia, post-partum bleeding, post-operative bleeds; and actually up to about 70 to 80 percent of patients have received red cell transfusions at some point in their lifetime, which really attests to the potential clinical severity of the situation.

The treatment for bleeding episodes very much depends on the type of bleeding. It can with local attempts such as compression or use of fibrin sealants, antifibrinolytic agents are also used, but the standard of treatment for severe or more serious bleeding episodes is really use of platelet transfusions. The adverse consequence of the platelet transfusions can be the development of antibodies, either to the HLA complex or to the glucoprotein

2B3A receptor, which is defective in this condition. This happens in about 35 to 40 percent of patients or potentially even more, and this means that this renders future platelet transfusions for therapy ineffective.

(Slide.)

With respect to congenital factor VII deficiency we heard the incidence is about one in 500,000 or so. The clinical manifestations are quite variable. They do not often correlate with the factor VII level in the plasma for reasons that are not completely understood at this point in time; and the clinical manifestations here are nosebleeds, menorrhagia, similar to some of the things that we see in Glanzmann's thrombasthenia, easy bruising. Twenty percent of patients have central nervous system or gastrointestinal bleeding, and the patients that have this it seems tend to present earlier in the course of the disease. Joint bleeds are rare, but they do occur, and treatment for bleeding episodes is dependent upon factor VII replacement therapy,

(Slide.)

This slide is really to illustrate the current treatment options available for the treatment of factor VII deficiency, starting with fresh-frozen plasma. The advantages of this product are that it is cheap and relatively easily available. The disadvantages are that in

some situations it may have limited effectiveness. It is unsuitable for surgery generally because of he small concentration of factor VII per unit of FFP. You tend to have to transfuse a lot of FFP, leading to circulatory overload in some patients, and some patients also develop allergic reactions to the product.

With respect to prothrombin complex concentrates, these are used for surgery; but as they contain other vitamin K-dependent clotting factors there is a risk of thrombosis that does need further characterization. Plasma-derived factor VII we know is available in Europe, not so far in the US. It is effective and able to be used for surgery, but as a plasma-derived product it does still have the potential risk for viral transmission.

The first two options are not FDA-approved. I mentioned that plasma-derived VII is not available in the US; and recombinant VIIa has been recently licensed for use in patients with congenital factor VII deficiency in Europe, and that is a product that is available in the US and it is occasionally used. It doesn’t have any risk of human pathogen transmission associated with it. But for disadvantages there is limited use, limited experience with use of recombinant VIIa in congenital factor VII deficiency, and the short half-life may limit use in prophylaxis,

although this is under investigation.

(Slide.)

So why does a company like Novo Nordisk pursue these indications? Well, first and foremost, there is an unmet medical need. The need in congenital factor VII deficiency to have a recombinant treatment option available to VII deficient patients as they are available for patients with factor VIII or factor IX deficiency. Also in Glanzmann's thrombasthenia as I mentioned if patients develop anti-platelet antibodies or become refractory to platelet transfusions the therapeutic options are really limited; and there may be HMLA matched platelets or cross-matched platelets that can be considered, but often these are not available when a patient has an acute bleeding episode.

We have also received encouragement from advisory committees such as the Medical and Scientific Advisory Committee for the National Hemophilia Association to pursue development of factor VII for Novo VII for use in deficiency. Also some agencies around the world, for example in the UK, the Hemophilia Directors Organization recommends Novo VII as treatment of choice for patients with congenital factor VII deficiency, even though it wasn't licensed in that indication at the time, and it is being used. We are aware that it is being used in these patients at doses that may be

inappropriate. They may be too high or too low. It would be nice to be able to evaluate the data and see if dosing recommendations or guidelines can be provided for physicians as well as to be able to collect relevant safety data.

(Slide.)

So this we have gone through over the past couple of days in terms of the -- this is the hierarchy of strength of evidence. We in these conditions are in the lower end of the scale. Glanzmann's thrombasthenia and VII deficiency, absolutely no exception.

(Slide.)

When we took a look at what data was available on Glanzmann's thrombasthenia -- the first point on the slide is not there to confuse you, but just to emphasize that the regulatory submission was specifically for patients who are refractory to platelets due to antibody formation. The company decided to file also based on encouragement from the medical company and positive feedback from a rapporteur in the European community. So looking at the data there was an observational study of four patients with 24 bleeding episodes. There was an international survey. There was actually a registry that was where information was collected on 59 patients with 108 bleeding episodes and 34 surgeries, and this registry was conducted with the goal of collecting

data concerning efficacy and safety for Nova VII use in Glanzmann's thrombasthenia, and handful of independent published reports.

(Slide.)

Now with the issue of controls group, in a population -- I am going to focus on Glanzmann's for the interest of time and because it is the rarer of the two disorders and it has some interesting things to discuss. Not really feasible in this population for the following reasons. First of all, the patients that become refractory to platelets, it is a very, very small number of patients, I think maybe around 40 percent; but also if you consider the number of patients that actually require hemostatic therapy for treatment of a bleeding episode that is also very small and unpredictable.

Recombinant VIIa is now recognized to be one the few therapeutic options for these patients. So there may be an issue about conducting trials where physicians may be reluctant to enroll their patients in a trial or the patients themselves perhaps they have been treated with VIIa before and are aware of the efficacy. They may also be reluctant to be included in that type of a trial. The point that was brought up yesterday, too, if there is effective treatment available, or potentially effective, it may be unethical to

treat patients in a situation that need it.

With respect to generation of historical control groups, that is also very difficult because really insufficient data exists to be able to do this. Within-patient controls are probably possible because the patients do bleed until treated and they can be assessed.

(Slide.)

With respect to endpoints, because of the variability in the type of bleeding episodes there is also variability of the criteria that is used for efficacy, and how do really define achievement of hemostasis in sort of a uniform fashion. With nosebleeds, you know, you can easily or more easily see the time to cessation of bleeding, but if you are trying to evaluate internal bleeds, GI bleeds or bruising, or even joint bleeds, it is a lot of more difficult. Sometimes looking at stabilization of something like hemoglobin level is often used because you can't really directly visualize the site of bleeding. Because this also looking at these observational studies there has been variability in the timing of the efficacy evaluation. Should it be looked at within six hours or within a longer period of time? So those have been challenges.

(Slide.)

With respect to the survey, the international

registry data that was published by Dr. Poon* and his group, there are challenges looking at the data with this, too. It is difficult to develop line listings or it is difficult to resolve discrepancies in the data because of the way that it was collected. So to enhance the understanding or understanding of the disease management we are considering developing a questionnaire to survey physician treatments of Glanzmann's thrombasthenia in cooperation with our medical advisors on the subject to really assess current treatment practices in the US, to evaluate investigator assessments of safety and efficacy, and to try to identify some issues and other challenges that we could think of when we consider how to consider the best data possible to look at this indication.

(Slide.)

So the challenges and considerations. As I mentioned, they have been small patient populations with unpredictable bleeding events, so controlled trials are extremely difficult. The variability of criteria used for efficacy, especially in the observational studies. The limitations on the data as I mentioned make it difficult to go back and resolve the discrepancies, and the heterogeneity of the treatment regimens used also tie in with the variability of the, you know, trying to define what your

efficacy endpoints are. We are also aware that a bias may exist where successful treatment outcomes may be more likely to be published than non-successful. So I think all of these points really illustrate the need for additional prospective evaluation of efficacy and safety in clinical practice through post-marketing surveillance.

(Slide.)

So Novo Nordisk has partnered with some physician groups to collect data on the management and treatment of complications both in factor VII deficiency and in Glanzmann's thrombasthenia. We have partnered with the International FVII Study Group that is based in Palermo, Italy to set up a VII treatment evaluation registry, the STER registry, and also with an international expert panel to set up a registry for Glanzmann's thrombasthenia.

(Slide.)

Both of these registries are commitments as part of the approval by EMEA, and they are both online registries created as I mentioned for the pharmaco-surveillance of Novo VII. The purpose is really to evaluate therapies for VII deficiency not only with respect to Novo VII, but other treatments such as fresh-frozen plasma and plasma-derived factor VII, and also to similarly for Glanzmann's thrombasthenia evaluate the use of VIIa as well as

antifibrinolytics and platelet transfusions. So we will be able to, the data will be there to look at a sort of a control group. This was brought up in discussion yesterday as a potential limitation of some of the registries, but this information would be able to be accessed or developed from this registry.

The data collection is in the form of a stringent efficacy evaluation and a detailed adverse event questionnaire, and for the patients with factor VII deficiency immunogenicity will also be measured. The time line, it is going to be until adequate efficacy and safety data have been collected as determined by the CHMP part of the European Medicines Agency or for a maximum of six years; and the enrollment of the centers just recently started, so I can't really give you an update of that at this point.

(Slide.)

These are just what the websites look like. This is the STER registry. It just gives you a little bit of information about the product and how to get involved.

(Slide.)

This is the Glanzmann's thrombasthenia registry. This registry is owned by Novo Nordisk and the data are available every two years for access and to look at and send to the regulatory authority.

(Slide.)

So in conclusion, Glanzmann's thrombasthenia and factor VII deficiency have several unmet medical needs without licensed therapy currently in the US; and alternatives to randomized controlled trials really are necessary, especially in situations where patients may be reluctant to participate in trials or physicians may be reluctant to put their patients in trials, or in situations as we have here with VIIa where it is sort of a rescue therapy for patients who have developed antibodies to platelets. Post-licensure registries we think can support continued safety surveillance, but early and especially frequent dialogue amongst pharma, physicians, and regulators may and will lead to improved development and more effective therapies. I thank you for your attention.

(Applause.)

DR. CHANG: Now the floor is open for questions.

MS. BAKER: Hi. Judith Baker from Los Angeles. Thank you. Question, your registries, are they available in the US?

DR. ROJKJAER: They are. You can access them from the US. It is an international registry.

MS. BAKER: Is there any formal procedure for participation?

DR. ROJKJAER: I am going to actually defer that question to our registry expert who is ---. He is up in the back.

MR. : Yes. You have to sign up on the website. You can sign up and then you will get all the information from the CRO who is taking care of all of the --- issues with this registry.

DR. CHANG: Okay. One more question.

MS. : I laud you setting up post-licensure information on the internet, and I think this is really important because a lot of our patients, the rare, rare, patients, are out in a place where they do not have access to an institutional informatics system. So as much as possible registries in post-licensure data collection that can be entered on the internet and, you know, electronically which is encrypted and everything else is really important and I think will allow a lot of very small centers to participate.

DR. CHANG: Donna, do you have a question?

DR. DiMICHELE: Just a quick one. Thanks, Lisa. I was interested in the fact that in your license application in Europe you were if I got this correctly, unable to use the registry data that was already being collected both for Glanzmann's and the huge international factor VII study, is that correct?

DR. RIJKJAER: No. Those were set up afterwards, so they were only set up after the approval. The approvals were granted last January.

DR. DiMICHELE: No, but there was an ongoing international registry run by Professor Mariani* in Italy for factor VII that has been ongoing for years.

DR. RIJKJAER: Yes, right.

DR. DiMICHELE: And there was a Glanzmann's registry by Dr. Poon that was ongoing for years prior to your application. So do I understand it correctly that the data was unavailable or un- sort of evaluable or non-evaluable with respect to your licensing application? Is that correct?

DR. RIJKJAER: No. Actually I think we did use some of the cases from the registry in the application. I didn't talk about the data specifically that we used for VII deficiency.

DR. DiMICHELE: So you were able to use the registry data.

DR. RIJKJAER: Yes.

DR. DiMICHELE: Okay, because that is obviously a very important point with respect to some of the information we are going to collect later. Okay.

DR. CHANG: We will have two speakers to cover antithrombin III from plasma-derived product. The first

speaker is Juan Oliveras, and he is a clinical pharmacist -- oh, you are the second one. Okay. I am sorry, and he will cover the antithrombin III that is manufactured from Grifols, and you will talk about characterization or --? Okay.

Antithrombin III Grifols: Characterization

Juan I. Jorquera, PhD

DR. OLIVERAS: Hello. Good morning. My name is Juan Jorquera and I am responsible for --- development at Grifols for plasma rare proteins. I am going to present the data on the drug that we have currently licensed in Europe. This is product is licensed in several countries in Europe, and that we are working to bring into the US market currently.

(Slide.)

From the point of view of plasma origin and testing, which is an important point for any --- approach, we work FDA licensed plasma centers, Qseal certified. All plasma is tested according to current regulations by the FDA and the European Pharmacopoeia, and furthermore all plasma is tested for hepatitis A, B, C, HIV, and virus B19 by --- testing.

(Slide.)

The process starts from frozen plasma and after cyroprecipitate supernantant and fraction I supernantant from

which we can start the pyrothrombin complex we obtain the fraction II and III supernatant and this is the intermediate that we employ for purification of antithrombin III.

(Slide.)

From this supernatant we perform a first affinity chromotography with --- and then we perform a pasteurization for viral inactivation. The material is submitted to a second affinity chromatography again with ---, and then we filter through a 15 --- filter to obtain the final product which is freeze dried.

(Slide.)

This is the formulation of the product. We have 500, 1,000, 1,500, and to sterilize we use mannitol ---.

(Slide.)

From the biochemical point of view it is a very pure product, 97.5 pure, also 98 is monomer form, and the AT activity is the one we intend to put in --- 50 units per ml.

(Slide.)

The --- the AT activity and the antigen, which is an important point since this is a pasteurized product, it is quite close to --- not to have a big impact after the pasteurization. It as 95 percent --- capacity, which is a point that we control basically. The --- activity approaches the --- maximum specific activity that one can

expect for antithrombin III, which is 7.8 or close to it.

(Slide.)

That is a typical profile of the --- electrophoresis. This peak corresponds to the native antithrombin III with the capacity to bind heparin, and this is electrophoresis showing also the --

DR. CHANG: You have to speak a little bit louder into the microphone.

DR. JORQUERA: Okay.

(Adjusting equipment.)

Okay. I will get closer to the microphone. Is this better now? Okay.

(Slide.)

These are two slides an isoelectric focusing. I think this is an important biochemical parameter for the product showing the natural variability of antithrombin III in human plasma with several types of --- to the molecule and the level of purity --- no additional --- antithrombin III and --- conditions.

(Slide.)

So what we did is we did a small comparison with what would be the conditions or --- versus the requirements of the United States pharmacopeia, also with the currently licensed products in the US market.

(Slide.)

So that we were in the range of the potency that the US pharmacopeia would require. The specific activity would be quite comparable to the specific activity of the existing product. In terms of monomer by HPLC, it would also be quite comparable, 95, 98 percent. The --- activity and the --- very similar, and the heparin binding capacity is also similar.

(Slide.)

This is a characterization of potential impurities that would be expected to be in the product depending on the --- for it, and as you can see essentially are under the --- in both products --- in one of the batches here. So if you compare with the concentration of antithrombin III the range of impurities is really negligible.

(Slide.)

This is also a comparison of the --- focusing pattern between the licensed product in lines two and three and the product that we manufacture.

(Slide.)

And also again comparing the specifications of the United States Pharmacopeia and licensed product. We see that our product will comply with the requirements of the pharmacopeia and also for the specifications of the already-

existing product. Essentially the same on all list of parameters including the --- licensed product specification. Again, some stabilizers, some maybe specific for ---. This is not working on the monitor. Maybe a specific stabilizer for --- product.

(Slide.)

From the point of view of viral safety which has already been mentioned very important for plasma-related products, we combine two --- activation steps. We combine pasteurization which is effective for all -- thank you -- all ---. I can't see it. Oh, and nanofiltration.

(Slide.)

Just to show you kinetics of viral inactivation by pasteurization of HIV. One would expect a very quick kinetic and --- is what really you can measure here.

(Slide.)

Also for the model of --- very quick inactivation in the very early stages of the pasteurization process.

(Slide.)

And even for --- a highly effective procedure with -- thank you. A very effective procedure with close to I think it is seven logs reduction of --- 10 hours of duration.

(Slide.)

This is a slide that we prepared showing the

comparative sizes of the plasma, all potential plasma-born viruses compared with a --- of the --- nanofilters that we employ for ---. So I think it speaks for itself around the capacity of reduction for any potential contamination.

(Slide.)

This is the table of reduction of --- validated steps that we have. I want to draw attention to the high value of ---.

(Slide.)

I am going to be also very fast here because I know we are late. We performed the non-clinical studies that are required for licensing of one of these products. We performed toxicological safety in rats, mice, rabbits, beagles, guinea pigs identifying targets for toxicity and so on. We performed the study with the precursor product of this antithrombin III which only had one --- purification step, so it would be a worst case with respect to the current product.

(Slide.)

We also did general pharmacology in mice, pharmacokinetics in rats, and some preclinical efficacy studies.

(Slide.)

In conclusion from the non-clinical program we came

to the conclusion that the absence of mortality in the preclinical studies and the lack of any confirmed relevant adverse sign affecting respiratory, circulatory, renal, and so on and so on, supported the safety of ATIIIDAF-DI to begin clinical trials in humans, and this product has been in the market now in Europe for close 13 years. Now my colleague will go into the clinical part.

Continuance of Presentation - Clinical

Juan Oliveras

MR. OLIVERAS: Hello. Good morning. I am Juan Oliveras and I am responsible for clinical trials at Grifols. (Slide.)

Well, I will show you the little clinical data we have with our product. So I think this is not my presentation.

(Adjusting equipment.)

Okay. I will show a little information on clinical data we have with this product, but first I would like to show you the history of this product. The first antithrombin III at Gifols was licensed in Europe in Germany in 1986 and it was licensed for both congenital and secondary deficiencies. The basis for the license was on clinical data from clinical trials that were done in the early ‘80s. These clinical trials include some clinical information about the

pharmacokinetic file in congenital deficiencies and also some data from secondary deficiencies.

Then the product had modification in the manufacturing process. This second formulation was ATIII-DAF because it did incorporate second --- affinity chromotography and is called Anbin in some countries. It was licensed in Germany in 1994 and then in other European countries.

Finally we introduced the nanofiltration as a second inactivation step. This product is called ATIII-DAF/DI or Anbinex and was licensed in Spain again as an amendment to the previous license in September, 2004, and the last month was also licensed in Germany and we expect the licensing in other countries. The clinical data we have with this third formulation was just a PK study in congenital deficiency.

(Slide.)

Yesterday Dr. --- explained to you a little bit about the --- requirements of the European Union for congenital deficiencies to license antithrombin III. This guide was then implemented in 2002 and basically they required to demonstrate that biological activity and the pharmacokinetic file are consistent with the published data. For that it is required a clinical trial, a pharmacokinetic clinical trial with 12 patients. There is no requirement to

make a formal clinical trial so we have to report all the clinical data we have on congenital deficiencies, and we have to also evaluate clinical safety.

(Slide.)

Our clinical trial was designed as a open-label, multi-center study. It participated four Italian centers, although some other centers also --- patients that were treated in the four investigator centers. We include patients with congenital antithrombin III deficiency with antithrombin levels below 60 percent. The dose was one single infusion of 50 to 60 international units per kilo to --- pharmacokinetic file, and then additional doses if clinically required by the patient. The follow-up was 15 days for the standard pharmacokinetic analysis and then a six-month -- six additional months after this infusion, and the period of study was between 1999 and 2001. This means that the trial was designed and performed before the European clinical guideline was implemented and even before the first draft was available.

(Slide.)

However, the design was very similar to the current European guidelines. The number of patients were 12 with antithrombin III levels below 60 percent. Candidates should be treated in the near future because of clinical reasons.

Patients should not have been in treatment with heparin during pharmacokinetic analysis, and another exclusion criteria was the presence of thrombophilia due to other causes other than antithrombin III deficiency.

The objectives were the recovery and the pharmacokinetic profile as surrogate markers of clinical efficacy, and secondary efficacy, the clinical and viral safety and also the clinical efficacy in the case of therapeutic administrations.

(Slide.)

Well, these are the results.

(Slide.)

But the important thing is the number of patients. I think I don't have a full set of slides in my presentation, but you have in your papers. Basically we have access to almost 200 patients that the investigators believe they fulfill the inclusion and exclusion criteria. Most of them refused to participate in the clinical trial because they don't want to participate in a clinical -- to receive a blood product, or because of the ---. You have to consider that patients with antithrombin III deficiencies, most of them don't receive treatment even during all his life. Other patients would not participate in the clinical trial because of the exclusion criteria or because the baseline levels were

not below 60 percent. Then again after three years of recruitment we were able to recruit only eight patients and the results I showed you before were the results for these eight patients.

(Slide.)

The in vivo recovery terminal antithrombin II half-life was similar to other values reported in the literature. Only one patient received antithrombin III because of clinical requirements. Even if one of the inclusion criteria was to --- to receive product in the near future, only one patient was admitted to a surgical procedure, and this surgical procedure was successful. There no related adverse events or relevant changes in vital signs, or other laboratory parameters related to the product.

(Slide.)

Finally this is the post-marketing experience we have with this product. For the former formulation the volume sales in the last 10 years since marketing in 1994 to May, 2005, was close to 500 million international units, and this information includes all use. As I told you, the product is licensed in Europe for both congenital and secondary deficiencies.

We have received to spontaneous reports of adverse reactions. This is not active pharmaco-vigilance. This is

just --- pharmaco-vigilance. This is records we have received from the physicians who have some adverse event. These two events were a transient episode of tachycardia and hypertension and a transfusion reaction consisting of chills and fever.

Regarding the new product, it was licensed in Spain in the middle of last year. We introduced it in the market at the end of last year, and until now we have distributed two million international units and there have been no adverse reactions reported.

(Slide.)

Okay. So as Dr. Jorquera said before, we are trying to introduce this product in the USA market, and also we need to provide further data to the European authorities because the former data was formed in the early ‘80s, and we are discussing a clinical trial with the FDA to initiate some. Thank you very much.

(Applause.)

DR. CHANG: Because of the interest of time we will just take one question. Again, we will still have an opportunity at the panel discussion session.

(No response.)

Opportunities and Challenges in Developing Recombinant Human Antithrombin for Treatment of

Hereditary AT Deficiency for the EU and US Markets

Richard Scotland

DR. CHANG: Okay. Our next speaker will be Dr. Scotland from GTC Biopharmaceuticals -- Biotherapeutics, I am sorry. The presentation title is "Opportunities and Challenges in Developing Recombinant Human Antithrombin for Treatment of Hereditary AT Deficiency for the EU and US Markets," and this is actually the only product in this workshop that comes from transgenic technology. Doctor.

(Adjusting equipment.)

DR. SCOTLAND: Okay. Well, excuse me. I would like to thank the organizers for convening this meeting and for inviting me to participate and speak here today. In particular it is a pleasure to be talking with you today in a section dealing with case studies. Case studies are typically described after an outcome is known. We at GTC are actually living these case studies right now as we try to get this product approved both in Europe and in the United States.

(Slide.)

Antithrombin is a single-chain glycoprotein consisting of 432 amino acids. It has four N-linked glycosylation sites and six cysteine residues with three disulfide bonds. The molecule as it exists in plasma exists

in alpha and beta forms where the alpha form has four N-linked -- where the glycosylation on four of the N-linked glycosylation sites, and the beta form has glycosylation that exists on three of the four glycosylation sites. The alpha form exists in plasma at about 85 to 90 percent of the total population of molecules; whereas the beta form exists in plasma at about 10 to 15 percent. The beta form is actually believed to be the more physiologically active in the preparation. It is a serine proteinase inhibitor that inhibits thrombin and factor Xa. When AT binds to heparin it creates a conformational change and 1,000-fold increase in inhibitory activity.

The therapeutic indications for which this product has been developed and registered around the world in various parts of the world include acquired AT deficiencies such disseminated intravascular coagulation and sepsis. Where this product is approved in various regions around the world for acquired AT deficiencies there is very little clinical data to support those indications. It is also approved in various reasons for the treatment of hereditary AT deficiency patients, and these patients require treatment during high risk situations such as surgery or pregnancy, labor and delivery. Okay. So these products have actually been approved many years ago.

(Slide.)

We are developing a recombinant form of human antithrombin. We have sought through the World Health Organization a nomenclature which is antithrombin alpha. That is an international nomenclature non-proprietary name for the product that has been granted to us. The alpha indicates that it is the first recombinant version of this particular protein.

The product is produced and purified from the milk of transgenic goats. We have a closed herd of goats which is maintained in the United States. This herd of goats is certified by the US Department of Agriculture to be scrapy-free, and scrapy is the goat version of BSE. Expression of the protein into the milk is regulated by a mammary gland promoter where we typically achieve anywhere from one to four grams per liter of protein. The protein is then purified from the milk matrix by a series of filtration and chromatography steps, and it also includes a viral inactivation step as well as nanofiltration.

We have actually conducted robust viral and TSE validation of the purification process, and if anybody wished to know I could actually give you the log reductions. I don’t have a slide that will tell you that on the virus that we have tested. We have tested a panel of viruses in this

viral validation studies that represent potential viruses that might exist in the goats and includes single-strand, double-strand, RNA/DNA type viruses. In terms of TSE validation we have actually conducted a study to actual validate that if we scrapy, which is the --- that appears in goats, that we would be able to remove it, and we have --- 11 log reduction.

(Slide.)

So this slide actually talks about why the recombinant reduction system relative to plasma, and walking through this if we just take the recombinant AT, the source is milk where we achieve milligram per ml of anywhere from two to four milligram per ml in the milk. A goat will contribute about 750 ml of milk per milking. These animals are milked twice a day. We can get approximately 600 donations per goat per year, which gives us approximately 450 liters of milk from which we can purify this recombinant protein.

The reason of this exercise is actually to give you an estimate of the numbers of donors or either plasma or milk that would be required to produce a single kilogram of this protein. This exercise assumes a 50-percent yield through the purification process. Looking at plasma where it is the amount of At in plasma is approximately 0.125 milligram per

ml where you get these various volumes, and donations it is either one to four. I gave a range. It depends on how many people are donating at any particular time. This points out you need either 14,500 or up to 58,000 individual donors to achieve a one-kilogram quantity of the protein.

(Slide.)

We are developing the product for hereditary AT deficiency, and this typical plasma levels of less than 60 percent are common in these patients. In pregnant patients in particular you will see excessively low levels, down around 30 percent. AT supplementation in these patients is only required during high-risk situations. At other times these patients are typically anticoagulated with other oral anticoagulants. Published prevalence estimates range anywhere from one in 2,000 upwards to one in 5,000. For purposes of estimating the patient population in Europe and in the United States I have assumed a one in 2,000 prevalence and assumed certain sizes of Europe, which is the complete European Union, and these are the numbers I calculated out. Anywhere from 175,000 to a 150,000 individuals that may have this condition. Again, remember, that is assuming a range from anywhere from one to 2,000.

Clearly this is a rare condition, and what makes it even more difficult in order for us to be able to conduct

clinical trials is to remember these patients don't require supplementation throughout their life. It is only when they have or undergo a high-risk situation such as pregnancy. So if one were to take these numbers of patients and estimate how many pregnant patients you would have available to you to do a clinical trial you could do some calculations, and your numbers would become very small very quickly. Again, the point of this slide is actually just to indicate that this is a rare condition and in this rare condition it would require infrequent treatment during the course of their lives.

(Slide.)

As we heard yesterday and also as we have heard a little bit earlier today, the EMEA in Europe -- I am going to talk about Europe now and I will talk about the United States in a little bit. In Europe the EMEA has issued guidance documents that are available to us to help us develop this product. This first guidance is on the clinical investigation of antithrombin products. It is important to note that within this guidance the guidance is applicable to both antithrombin derived from plasma as well as other recombinant products. So we have guidance from EMEA as to what is needed. We heard a little bit about that already. The EMEA has also issue guidance on the clinical investigation of these products in the case that you need to

demonstrate reduction or prevention of venous thrombotic events.

So at the end of the end of the day, the clinical development program for AT requires the clinical pharmacokinetic study of in AT patients as we have heard earlier. These patients are not undergoing a high-risk event, so the data that you derive from that is simply pharmacokinetic data in a patient population that have low levels. But they are not in a high-risk situation, so it does not really mimic what you are going to see in a clinical situation. As we heard earlier, if you are not able to demonstrate consistency in terms of activity or pharmacokinetics, then one would need to do a open-label safety and efficacy study.

If could just comment a bit on the demonstration of consistency of AT activity in pharmacokinetics, if one looks at what is in the published literature relating to the pharmacokinetics of plasma AT you would find a number of papers that provide you with very, very broad ranges of data. So if one wanted to say one was consistent with the published data, one could easily do that if they just wished to select certain data.

(Slide.)

So in addition to the guidance documents we have

also sought scientific advice from the EMEA, and on the basis of that advice, again it is pretty much so consistent with the guidance documents, we needed to do a pharmacokinetic study, and the purpose of this study is to estimate what you might need in an actual clinical situation. Because the pharmacokinetics of recombinant AT is different from the plasma-derived products, we actually modeled the data from the study to derive a dosing regimen that we believe would work in this open-label safety and efficacy study. The guidance that we received from the EMEA at the time again was we needed to treat at least 12 patients and we needed to use an objective measure of efficacy. In this case we used duplex ultraserial duplex ultrasound of these patients, and to avoid any influence of bias the data were reviewed by an independent review of an independent body of individuals who could read these data. Then the scientific advice told us that any non-zero event needed to be carefully explained.

(Slide.)

This is an overview of the study. In this case we indicate 15 AT deficient patients who had documented At activity levels of less than 6o percent and a personal or family history of thrombotic complications. This particular issue of whether or not a patient has personal or familial history is important, and I will talk about that a little bit

later when we talk about clinical trial designs and the ability to enroll patients. These patients needed to be scheduled for elective procedure. That is either surgery, C-section, or induced or spontaneous delivery.

Efficacy was assessed. What we are looking at is the incidence of DVT as well as the incidence of other thromboembolic complications in addition to safety, and that is adverse events and immunogenicity.

(Slide.)

I will talk a little bit about the patient recruitment effort that we had to undertake in order to enroll these patients into this study. It was actually a multi-national effort where we contacted individuals in 16 different countries around the world. We had contact with greater than 23,000 physicians. There is no patient registry, so we had to go out and try to find these patients. First we had to find the physicians who treat the patients, and as you can see from 23,000 physicians who we had contact with, we identified 500 physicians who have had HD patients in their population. We simply notified them. We asked if they had patients; we would be happy to talk to them. The patient recruitment period for this safety and efficacy study was 18 months. Remember we enrolled 14 patients. That is clearly less than one patient per month.

(Slide.)

A little bit more information about the patient recruitment effort. This is the number of countries where we enrolled patients, the number of sites we contacted, the number of patients that might be eligible for enrollment into the study, and the actual number of patients that were enrolled. What is important to note out of this is approximately 17 percent of the patients that we identified were enrolled into this study. Reasons for inability or we couldn't get these other patients for example into the study, it could have been results of time to regulatory filing in a specific country, time to IRB or ethics committee approval, if it was an elective surgery that was scheduled we didn't have three months or four months, and if we had to go to through the regulatory as well as the IRB and ethics committee approvals we would miss those patients. So it is clearly difficult to identify and recruit, enroll and treat, and evaluate these patients.

(Slide.)

So in summary, the clinical development time line for this particular program was approximately 28 months. That is from the first patient in in the human PK study through the last patient out in the safety and efficacy study. We have submitted a marketing authorization to the

European Medicines Agency in January, 2004. We have had dialogue with the agency in the intervening period, and we have most recently received a list of outstanding issues from them which we plan to reply to by July 25th. In addition to that, we will be hosting inspectors from EMEA who will be visiting us at our farm in Massachusetts later this summer.

(Slide.)

Okay. Now if I could just turn my attention to the United States and what we are trying to do here. As we heard yesterday from Dr. Silverman and others, adequate and well-controlled trials are required. But before embarking on this exercise, it is important for people to understand what we did, and what we did is we commissioned a study with an evidence-based medical practice center here in the United States to actually scour the published literature on antithrombin to provide us with as much information as we could. This study was done in an unbiased way. It was done according to a protocol that people would go in and select literature based on a predefined protocol, and the bottom line on this was we wanted to understand a little bit about the efficacy of the product since it is a rare disease.

There were approximately 81 patients identified in the published literature, and of those 81 patients from what we could tell none of the patients had reported a thrombotic

event. There is of course the potential for bias in the reporting of the published literature, but that is what the published literature tells us, and that is pretty much, though, consistent with what we know from the clinical trial data we have heard to date.

So in terms of what could we do, we actually walked through the process of what type of control we might be able to use. Placebo controlled, we ruled that out because of the known high risks to these patients. In particular, if you are treating a pregnant woman, a young, pregnant woman, you would not want to subject her to a failure to treat. Also it is just the large sample sizes.

In terms of active comparators what we needed to do is we needed to decide whether or not we were going to do -- if we could do this -- do a superior or non-inferiority type trial. Then with regard to active comparator, there were two options available to us. That is no treatment, no AT treatment, which means we would have had to employ a standard of care in this patient population. We actually evaluated that and we actually came to the conclusion that there is no given standard of care in the absence of treatment with AT. So we ruled that out primarily because of the inability to identify a standard of care or to impose one upon physicians, and also it would have required phase II and phase III

studies. That would have been, because of the enrollment period, would have been measured in decades, not years. Decades to enroll these patients, it is not feasible.

We also looked at the possibility of doing a non-inferiority study. We ruled that out again because of a large sample size and the availability of a comparator product care in the United States. Thrombate is the only product that is available. It has been available intermittently. To actually embark on a study and not be able to guarantee one be able to have the product is foolhardy at best. So it leaves us with historical control, and that is AT in a non=inferiority.

(Slide.)

So we had extensive discussions with the agency as to how we might be able to do this, and what it really comes down to at the end of the day is what is feasible. Feasible being what it is one can do given within certain limits. This is the only feasible study design available to us if we are going to be held to the standard of having an adequate and well-controlled trial.

In this particular case the comparator will be human plasma AT treated patients. These data will be collected from medical charts. It will require a multi-national effort to identify the sites and these contact these

physicians, and actually get into the medical charts and collect the data. In addition to that, with the work that we have done to support our submission in Europe, it will require additional study where we will need to treat an additional 17 patients. So again, we are going to be on a treadmill to try to identify and recruit and enroll these patients within a given period of time. It is going to be a multi-national effort again. These two studies, and the historical control and the active controls -- the active arms, will be separate protocols that we can run simultaneously.

I will just leave it now to indicate to you that the study is underway in the United States, and I hope I have an opportunity to talk to you again in perhaps a year's time or two year's time to give you an update as to where we have ended, both in Europe and in the United States. Thank you.

(Applause.)

DR. CHANG; Let's just take one question.

DR. PEYVANDI: Thank you very much for this very interesting report, but I was wondering what is the cost of the production of this type of product comparing to the normal recombinant protein.

DR. SCOTLAND: Okay. Well, I can't really talk to you too much about cost per unit. But what I can tell you is

cost to us has been fairly significant because we have had to establish a farm, we have had to establish a closed herd of animals, and I actually should have pointed out that the vast majority of animals that we now have on the farm today are actually imported from New Zealand where these animals -- where the herd -- it is actually scrapies has never been known to exist. At the end of the day we are going to have to be cost competitive, and we should be able to do that provided that the clinical trials that we have to conduct and the assurance that we can actually get something through the regulatory process is going to be kept at a reasonable level. If one has significant delays all those costs of maintaining those animals and having people around them to care for them and everything else just drives the cost right through the roof. So it is --

MR. : You use New Zealand donors for an American market?

DR. SCOTLAND: I am sorry. I missed that one.

MR. : ---. (Away from mic.)

DR. SCOTLAND: Okay.

DR. CHANG: I am going to take a liberty as a chairperson for this session that we are going to have a break now. We had a long session this morning, and then let’s take a 10-minute break and then come back at a quarter

to 11:00 and we will start with the last presentation on this session before the open panel discussion. A quick announcement that we have a handout, a new handout outside of this room which is provided by Dr. Rainer Seitz. It is a new draft guidance entitled "Guideline for Clinical Trials in Small Populations," and welcome to have a copy.

(Whereupon, a short break was taken.)

Experience with Accelerated Approval for Fabrazyme

Alison Lawton

DR. CHANG: On case study is going to be presented by Dr. Alison Lawton. The title of her presentation is "Experience with Accelerated Approval for Fabrazyme." Am I pronouncing --? Fabrazyme. Welcome.

MS. LAWTON: First of all I have to say I am glad that you have all had your caffeine so you won't fall asleep -- hopefully you won't fall asleep -- during this presentation. I have to say I feel a little bit of an imposter, because I am not going to be talking about any rare plasma protein disorder. Fabrazyme is for Fabrey disease, but I think hopefully during my presentation you will see there are a lot of similarities, and so I think I have been asked to talk so you can see what we have done on a very rare disorder and how we have managed to use the accelerated approval mechanism to get approval. I am also going to run

through my slides very quickly to try and make sure that we don't stay so far behind. So I apologize if I go fairly quickly.

(Slide.)

So what I am going to talk about is I am going to give you an introduction to Fabry disease. I am going to tell you a little bit about the product, Fabrazyme. Then really most of the presentation is going to be on the clinical development challenges that we faced and some of the lessons learned, which I think as I said earlier are very applicable to some of the same challenges that you are facing.

(Slide.)

So Fabry disease is a rare, lethal, x-linked inborn error of metabolism, and to give you an idea when I say rare I thought it was interesting this morning during the presentation I heard hyper-orphan, super-orphan, and I like to refer to it as ultra-orphan.

(Laughter.)

So there are three different names there. Maybe we should come up with some consistency there. But Genzyme tends to talk about ultra-orphan as meaning less than 5,000 patient. To give you an idea for Fabry disease worldwide there are only 3- to 5,000 patients. Just to confirm that

even further since we had approval of a treatment for Fabry disease worldwide we only have 1,500 patients on treatment in about three years of the treatment being available, and here in the US it is just a little over 500 patients and the treatment has been available for two years. So it really highlights the limited number of patients.

So Fabry disease is basically a patient is deficient in an enzyme called alpha-galactosidase-A activity, and this enzyme or a-GAL-A as I will refer to it, basically its role is to break down globotriaosylceramide, and I am not going to say that again. You don't want me to struggle every time I say that word, so I am going to say GL-3. What happens is that glyco single lipid accumulates in various different cell types in the body and in the different tissues, and that ends up in end organ impairment. One of the things that we collected a lot of information on which actually supported where we ended up going when choosing our endpoint was that the accumulation of this GL-3 is particularly key in the vascular endothelial and how that deposits there and how that causes end organ damage, and I will come to that shortly.

(Slide.)

This is just a cartoon showing you Fabry disease compared to something like hypercholesterolemia. Very

similar in that the pathology continues over the lifetime. You get over time more and more increase in the GL-3 levels in the different cell tissues and tissues, but of course you don't necessarily get clinical symptoms until you get to that point where there is damage occurs and then you start to see a drop-off or you see the clinical symptoms.

(Slide.)

To go through some of the clinical manifestations in Fabry patients, one of the things is in these patients there is really a lot of heterogeneity across the patients and very multi-faceted clinical symptoms of the disease. So in many patients they can get pain crises in the earlier decades, usually before the second, third decades of life. Those pain crises actually go away, and what happens is you start to see renal failure and drop in renal function in the third decade onwards of life. Also CNS disease, so stroke as material collects in the CNS, and also cardiac disease.

(Slide.)

So what is Fabrazyme? Fabrazyme is basically a recombinant version of the enzyme that these patients are deficient in, recombinant human agalsidase, and of course we have data that shows in vitro and in animal models that that enzyme activity catalyzes hydrolysis of the GL3, which is the glycosphingolipid that is building up in these patients.

Fabrazyme was developed as an enzyme replacement therapy for long-term therapy in these patients, and we also were able to show that it is taken up by the lysosome at least in part due to the monnose-6-phosphate receptors on the lysosomes. That was obviously very important for clearing the GL-3 from the different cells.

We obtained orphan designation for this product, and we also did -- by the way, my presentation I am focusing on what we did here in the US. I will briefly touch at the end on what happened in Europe so you can see the differences there. I should also tell you when we filed the BLA, we filed the BLA for Fabrazyme in 2000. It was a fast-track product, priority review, which as you know priority review should be six months review time. So from June, 2000, it actually took us until April of 2003 before we received approval, and I am going to tell you why with some of the challenges we faced along the way from the clinical perspective. We also for compete disclosure I will also tell you that it was the first time ever I think in the history of the FDA that they had two BLAs filed within a week of each other for two different recombinant enzymes for the same orphan disease, and so that did not facilitate the review process here. It certainly complicated issues, so that I am sure had some implication at least on the time line as well.

(Slide.)

So the clinical review challenges. In thinking about what were we going to study for the clinical endpoint for our pivotal study given that there are very few patients. You know, a lot of different clinical manifestations, wide heterogeneity in the patients, how were we going to decide what we would study.

(Slide.)

We looked at a number of different clinical endpoints. First of all we looked at pain reduction, because pain at least would be a relative short-term endpoint to look at. The trouble is with pain is we all know it is very difficult as far as it is subjective. You need a large clinical placebo-controlled clinical study to be able to study pain. But what made it even more difficult was that in Fabry disease itself the pain wanes over time, and so we couldn't know when we were enrolling patients at what point they were, whether their pain was about to drop off and go away or not, and that impacted how we could enroll patients. We also because of the pain in the extremities mainly for Fabry disease, we weren't even convinced that the usual validated pain instruments would be appropriate for measuring what we needed to in Fabry patients. Then of course very importantly the numbers of patients that we would have needed

to able to show statistical significance on the pain endpoint was really just -- it was just not feasible in this Fabry patient population. As I mentioned earlier, the pain, not all patients get pain. It wanes over time, and so a very small subset of Fabry patients at any time would have pain in order to enroll into these studies.

(Slide.)

We also looked at cardiac and cerebrovascular events as something we could look at in these patients, and of course again thinking about how, what kind of sample size, and the duration of the study we would have to do here. We would have to study patients probably over some decades to be able to see a difference. Again, do you catch people early and try and show that you have stabilized the disease, which would certainly take many, many years to study; or do you try to catch them when they are on the downward spiral and starting to show clinical manifestations, which means probably a lot of damage has already been done which is irreversible and that is not necessarily the best patient population to study. So there were many challenges here as well. One of the key issues, and I have heard it from all of the presentations again this morning, is there was a real lack of historical data and understanding of the progression of this disease. So we didn't have the event rates. We

couldn’t even take a guess on what they might be to start to think about powering the study. Of course with something like cardiac and cerebrovascular events other conditions such as hypercholesterolemia and hypertension really would probably end up impacting things more than the Fabry disease, and we wouldn’t be measuring what we really were trying to.

(Slide.)

Renal function, we looked at renal function as well. Again I talked about how many in many cases if you catch it too late the damage is already done and it is irreversible, so that was a challenge. The fact that the renal function can remain normal for many years and then decline very quickly, and again thinking about the size of the study that we would need and with the placebo-controlled, the duration and the size of the trial. We really decided that none of these clinical endpoints were feasible in this patient population.

(Slide.)

So what did we do? And I apologize. This says accelerated approval regulations subpart H. I apologize. I recognize that is the drug. It should say subpart E as well as subpart H. For Fabrazyme it was actually subpart E because it was a biologic.

(Slide.)

As you know, accelerated approval is for products that treat serious or life-threatening illnesses. The therapy has to show a meaningful benefit over existing treatments, and the use of a surrogate endpoint for accelerated approval has to be reasonably likely based on pathophysiological or other evidence to predict clinical benefit. This last point is a key point that I want to come back to.

(Slide.)

So we thought about this for Fabry disease and Fabrazyme and we felt, yes, Fabry disease is certainly progressive and it is a fatal disease. There really isn't any current therapies prior to Fabrazyme. There are only palliatives, so pain relievers for the pain. People used ACE inhibitors for the renal aspects. We felt that there was enough information about the pathophysiology of the disease that would support showing if we could reduce the GL-3 accumulation to normal or near normal levels that that really would be predictive of clinical benefit, but this was a key piece that ended up taking us a lot longer and requiring a lot more data than we ever dreamt we would need even just to show that this surrogate endpoint was appropriate.

(Slide.)

So the surrogate endpoint that we chose was, as I

said, the reduction of GL-3 in the renal capillary endothelials down to essentially normal levels after 20 weeks of treatment with Fabrazyme. One of the things we had to do is we had to develop a specific scoring system, and we looked at how we did the morphologic using light microscopy. We used three blinded independent pathologists who did the assessments using this scoring system. Again, how we did this scoring system, the details around how we developed that was another very key aspect that again going into this we were a little naive about how much detail would need to be available and how we developed that scoring system.

(Slide.)

The rationale was that the renal failure was certainly the most common devastating feature of the disease. We had a lot of information as I say that we started to build to show that the buildup of the GL-3 in the vascular endothelial was really the pathologic basis for morbidity and mortality, and I will show you in the next slide. We had some data from different variants of Fabry disease, different genetic makeups, and what we call the cardiac variants in the female heterozygotes who were less systematic than the standard Fabry homozygous patients. We could obviously study this surrogate endpoint in a reasonable time frame and the sample size was a reasonable size to actually do a study in

this patient population. As I mentioned earlier, our scoring that we developed for the microscopic assessment was really a key piece.

(Slide.)

So this slide just shows this here. The top is endothelial cell involvement, and the bar charts show whether there is accumulation of GL-3. The bottom bars show epithelial cell involvement. Remember it was a vascular endothelial cell that we decided to choose as the surrogate endpoint here, and on the right-hand side are the typical hemizygote Fabry patients who are markedly symptomatic. They have considerable epithelial as well as vascular endothelial buildup of GL-3. However in female heterozygotes or cardiac variants who are mildly symptomatic we found that they had very little buildup of GL-3 in the vascular endothelial cell, and likewise female heterozygotes who were asymptomatic had no buildup of GL-3 in the vascular endothelial cells. I will come back to this chart in just one moment.

(Slide.)

This is very quickly just to show you what we got in our pivotal study, the results. Basically the scale here is the percent of zero scores. So remember the zero score, the microscopic assessment, basically shows that the GL-3 levels were down to normal or near normal, and this was the

20-week pivotal study. The placebo patients had -- zero patients had reduction in GL-3 to a zero score, whereas 69 percent of the patients who received Fabrazyme had reduction in the score down to a zero. This second half of the slide shows that after the pivotal study was complete we continued treatment. We put the placebo patients on the Fabrazyme, and after six months of treatment 100 percent of those patients now had reduction of GL-3 down to a zero score. For the patients who had already been on Fabrazyme, when they continued for another six months the number of patients whose GL-3 was reduced went from 69 percent to 92 percent. So this was really the key result of our pivotal study, statistically significant, that gave us what we needed to move forward and file the BLA.

(Slide.)

Just to show you briefly what we -- this is the same slide, and what we showed then was after Fabrazyme treatment by reducing the vascular endothelial cell buildup of GL-3, we were able to shift patients who were markedly symptomatic to look more like patients who are either mildly or asymptomatic.

(Slide.)

So one of the things, that was the pivotal study. That is what we filed our BLA on. One of the things, as you

all know, for accelerated approval, one of the key things is what does the clinical study look like in which you are going to verify and confirm the clinical benefit. This was something we really struggled with during both prior to the BLA and during the review cycle.

(Slide.)

First of all of course, what would the control study need to look like. The key thing was what control could we use. We felt at that time that given the data that we had on the surrogate endpoint that it was just not ethical to do a placebo controlled study in these patients, and as a result we went out and conducted a significant study where we went back, got informed consent from patients to go back through their medical records and collect considerable natural history on these Fabry patients. However, this still was not enough to use that data as our control data, and that really delayed us significantly because we felt that collecting that data and using that, that we could use that as the control and then have an open-label study that we compared back to the historical data. Unfortunately we just weren't able to get enough historical data that was strong enough to design our clinical benefit study that way. So what it meant was the only option we had ended up being we had to do a placebo control study for the clinical benefit

study, and this of course had many challenges in itself.

(Slide.)

So just to tell you quickly what the clinical benefit study ended up being was we were looking at the effectiveness of Fabrazyme versus placebo in prolonging the time to any clinically-significant deterioration in the various organs in which the GL-3 could build up. So we looked at renal function, cardiac function, CNS, and basically death from any other cause. Originally we had just wanted to look at renal function, but it was felt again that that was just taking one aspect of the disease that may not be applicable to all patients because of the other manifestations. So we had to include all of these different endpoints, and the goal was to compare the Fabrazyme versus the placebo groups in the time to first clinical event. This meant that this study, remember, for accelerated approval would be in a post-approval stage. So Fabrazyme would be available to Fabry patients, and yet here we had a placebo control study that we would try to keep patients in the study knowing that they had a possibility that they were on placebo. This was a huge challenge to be able to do this and a great limiting step because of how far down that study did we need to be in order to make sure that we could indeed complete the study and get what we needed to confirm the

clinical benefit.

(Slide.)

One of the key things that I will mention to you -- I am not going to go through all of this slide. This just shows the actual clinical events that we listed under events of cardiac, renal, and cerbrovascular. I think one of the key things though is for any of you who know about studies in renal disease, normally studies require a doubling in serum creatinine as an endpoint. In this particular case it was felt that it was really just it was just unethical to let patients get to a point where their serum creatinine doubled and they were basically it was too late to switch them to treatment and to save them at that point. So we did spend a lot of time in discussion with FDA, and we came to agreement that at least a 33 percent increase in serum creatinine was more appropriate so that at that point if a patient's renal function was declining to that point that we could switch them over and hopefully put them on treatment to prevent any further damage. So that was a very important piece that we were able to come to agreement on.

(Slide.)

So challenges with the study, I mentioned the disease itself was very rare. One of the things we had to do, and this of course with any heterogenous population like

this, we had to actually set up a very narrow inclusion criteria for the serum creatinine in these patients entering this study because we wanted to catch them before it was too far. This resulted in a very high screen failure rate of about 67 percent. So we screened 252 patients at 41 sites in nine countries in order to get 82 patients who actually were enrolled in the study at 23 sites in six countries to be able to get enough patients to power this study that we needed to do.

I mentioned the issue about the placebo controlled trial in a commercial setting, and one of the things that I also want to highlight is in the accelerated approval regulations it talks about a study to confirm benefit is usually underway at the time of approval. So for this particular study we had to make sure not only that we had all of the patients enrolled into the study, but then a whole question about could we keep the study going was a huge discussion that we went -- we really struggled with, both Genzyme and FDA together, because we wanted the study to be successful to show us a clinical outcome, and yet we felt very strongly this treatment shouldn't be held back from patients having the availability. So we worked very closely with the patient association, with the patients themselves, with the physicians, and really I think the patient

association did a wonderful job in really talking and educating all of their members around for people who were enrolled in the study how important it was for the whole Fabry population at large to stay in the study.

The study itself was about three -- I think it was three years, a little over three years in duration, and one of the reasons I think it took us so long to get to approval was that we needed to know that the patients had been in at least for some duration before approval was given and everybody started dropping out. So that was a real struggle and I think one of the rate limiting steps in this program, and that is certainly a lesson learned for me about thinking early about how you are going to do your clinical benefit study and making sure that is underway and having those discussions early.

(Slide.)

This slide just shows very briefly, I am not going to go through it, all the different clinical studies. If you consider we filed in 2000, we were just putting patients who had been in the phase I/II on treatment. We were doing a study in Japan, bridging study for approval in Japan. But these are all of the other studies that we then had to establish during the process. I will tell you that in Europe we got approval again under exceptional circumstances, as

many of you have talked about this morning, about 18 months ahead of the US. So our clinical benefits study, the post-approval study required for accelerated approval, we were not allowed to have European sites because we were told it was unethical and they would not allow patients to enter a placebo-controlled study given that they had approved the product. So we had to do it in countries outside of the EU, although I will tell you of course the Europeans were very interested in the data we collected from that study. We recently submitted. We were able to complete that study with only five patients dropping out, and there is a little bit of a catch 22 because we really struggled with whether it was ethical and whether we could really do that study. We pulled out all the stops to make sure we were able to do it.

And I say a catch 22 because the trouble is now we have done it and now is that going to be a standard to do again. I really challenge everyone to think carefully about is that the route to go, because although it gives us, you know, the best data, I am not convinced from an ethical perspective whether that is really the best way to go. But it is a really difficult decision.

(Slide.)

So lessons learned. First of all, understand the disease. The collection of natural history data, you have

all said it here this morning. At Genzyme we are actually on our next enzyme replacement therapy for a lysosomal storage disorder called Pompey disease, which is even more rare than Fabry disease. I can tell you that first thing we did before we did any clinical study is we started collecting -- we did some major natural history studies to collect information, and that has been ongoing and that has been invaluable to how we then developed our clinical protocols. Always study a clinical endpoint unless it is absolutely impossible. You know, I wonder looking back. We thought the surrogate endpoint was the way to go, was a faster route, was an appropriate route for the sake of the patients. But looking back, we probably could have done the renal study or the clinical outcome study in the same time as it finally took us to get the BLA approved, so I am not sure which route I would go next time.

If the surrogate endpoint is really necessary because you can't study those clinical endpoints, then one of the things I talked about is you need a lot of data, and it comes back to your natural history data again. Even just to support the correlation of the surrogate marker that you are picking, correlate with clinical outcomes. In this particular case we felt very strongly it was the basis of the pathology of the disease. We felt we had chosen a very good

surrogate marker, but there was a lot of discussion still about data to support that and making sure that everybody was comfortable with it.

Even the methodology of how we measured the reduction in GL-3, as I said, we used outside consultants. We had renal experts. We had renal pathologists work with us in how they were going to score and what reduction was, you know, the same or equivalent to normal, how that was going to be scored. Those details ended up certainly in at least two of our review cycles were major questions that we had to address in order to make sure that, again, people were comfortable with that information.

Prepare early for the confirmatory study I talked about, and of course the whole issue of the feasibility of completing a placebo controlled study in a post-approval setting is a huge challenge.

(Slide.)

There is one additional slide I have added which is not in your package. As I was thinking some more, one of the things I think is very important is Genzyme before Fabrazyme we had a product called Cerezyme, which was again an enzyme replacement therapy, a recombinant protein for a rare disease called Gaucher disease. We had established a registry. We had over a decade of data on about 3,000 patients for

Gaucher, so a very high percentage of worldwide patients. We have data on patients who were treated as well as patients who were not treated, and that database has been a huge source of information as far as the long-term benefit and safety of Cerezyme. I think that in our discussions with the FDA knowing that we were willing to do a same kind of registry for Fabrazyme, we also did it for another product called Aldurazyme, and we have already started our registry for our next product, Miozyme*, well before we are thinking about filing the BLA. I think that has been really an advantage to us that we have been willing to do that and a very important source of data.

Timing of the advisory committee. I think this was a little bit of frustration on my part that I still wonder if we can't use the advisory committee process earlier to get advice on what we should be doing in these diseases. Rather than struggling through what we should be doing together as the sponsor and the FDA, coming up with the plan, and then you take your results to the advisory committee and they don't necessarily agree with what you have decided to do. Wouldn't it be nice if we got some experts there for example in this case and ask them early, "Do you agree with this surrogate endpoint? Do you think if we change the underlying pathology of the disease by showing reduction in GL-3 would

that be enough for you as experts who treat these patients?" I think that is a real something that I can continue to feel very strongly I think is an opportunity I think for us to improve.

Then lastly, the challenges with the clinical study populations versus the label in these very heterogeneous diseases. Again as you know, for a clinical study you have to have very narrow inclusion/exclusion criteria. So do you have a homogeneous population where you can show what impact your product has, and yet the actual population you are going to be treating with these therapies is very heterogeneous, and how do you cope with that? I think do you get broad, do you show efficacy and safety in a small group and then get broad label? Or do you just get narrow label and then more post-approval commitments? There is a limit as to how much people can do. Again, I heard many questions about the cost, and I think that is really if there is too much there then these companies just won't develop these therapies, and that is I think another challenge. This is also something I think for discussion with advisory committees is a great topic as well to try to get their input potentially or experts. It doesn't have to be an advisory committee, just getting the experts. In these types of diseases there are very few experts as well, and so the issue, you know, the whole issue

of who can sit on advisory committees is often you are using those very experts to help you design the clinical studies, and then are the independent to be on the advisory committees. That is a whole other challenge we have ahead of us as well. So with that, I think I will stop and take any questions.

(Applause.)

DR. CHANG: Thank you for the excellent presentation. So I have one hand up, one question.

DR. WALTON: Paul Walton from ZLB Behring. It is pretty clear from your presentation that Genzyme has a strategic commitment to these rare enzyme replacement diseases; and I wanted to ask one would suppose that would be on the basis that you would have profitable business cases, or, if not, what is driving the effort?

MS. LAWTON: I would say, I mean, obviously Genzyme's success as a company originally was based on Gaucher disease and enzyme replacement for Gaucher disease, and we do charge a lot of money for our therapies because they are very expensive to develop. However, I would also say that Genzyme has changed considerably as a company. We have many other products in much larger populations now. But as a company, we still have a total commitment to small patient populations with unmet medical need, and that is

still very much a core value and it is part of our culture that is very important to us that we are able to continue to develop therapies for those patients.

DR. CHANG: Let's take one more question.

MS. : What happened to the other product that came to the FDA at the same time? I think this is a big issue. Does one company know that another company is working on something, and what happens when there are competing orphan products?

MS. LAWTON: I think it is a good question, and I can tell you two very different outcomes in two different regions. In Europe both products were approved at the same time. I will also tell you that the other company took a completely different approach to their clinical development and their clinical studies. They decided to choose pain as their clinical endpoint, so a very different approach to us. In Europe both products were approved. In the US Fabrazyme only was approved. Both products were taken to the same advisory committee, one day after the other, and the advisory committee reviewed the strength of both products and the data presented, and the decision was made the Fabrazyme should be approved. The dosing of those two products are very different as well. Fabrazyme is dosed at a much higher dose than the other product.

DR. CHANG: I think I am gong to close the session, close the presentation session of this case study. I am going to give the podium to Dr. Keith Hoots to chair the open-panel discussion. I saw some hands up, and we will still have a chance to ask a question to all speakers. The speakers for the morning session please take the chair.

Open Panel Discussion

Keith Hoots, MD, Session Chair

DR. HOOTS: Thank you, Andrew, and it is a pleasure to be here. While the speakers are coming up I thought I would just try to -- there has been a lot of information disseminated obviously, and it is kind of hard to focus discussion in such a breadth. So I thought I would take a minute to try and do that by kind of challenging the panelists and the audience with one more scenario, which is not a true scenario, but could be.

Before I do that, I think it is important to remember that in terms of law jurists say that rare cases make bad law. So I think we all agree that for everyday products the types of requirements for licensure should remain very high standard and would not necessarily be adaptable in extreme cases perhaps because no product would ever be brought as we have heard over the last two days.

In addition, before I give you this scenario I

might say I have my own suggestion for the lexicon. I think probably we could call these all the way from milli-rare to -- all the way up to nano-rare. And really where there are only few cases per billion in the population and it is at the extreme, since it makes poor law that I wanted to give you kind of a scenario for what I would like to see for the extreme cases like a couple of the ones like protein C. The scenario is for protein S which is even rarer than protein C, and for what is the likely of somebody developing a product is probably minimally low, but it is actually based on a true scenario.

I was referred a patient with diagnosed protein S deficiency who was bilaterally blind from her protein S deficiency and was already on plasma replacement for that. The mother then subsequently a couple years later became pregnant, assured us that it was different father. Since it is an autosomal recessive disease we were pretty confident that the worst thing we had to worry about was heterozygous disease.

As luck would have it, that baby was born premature, and to confound the picture developed necrotizing enterocolitis. Well, we thought perhaps that was related to the stress of being premature and having heterozygosity. Started fresh-frozen plasma and got the child through the

scenario.

Because of what we had learned from the first child and because in the literature we knew that as you have heard from protein C deficiency that the --- findings are most profound in these kids and obviously the first child was completely blind. So our ophthalmologist was following this child daily for any retinal changes, and in fact we then began to as the child began recovering from the necrotizing enterocolitis began lengthening the time between the transfusions of plasma trying to get out to where the child would not need such transfusions. Lo and behold, about five days after one transfusion the ophthalmologist started seeing changes in the retina. By the time we got that baby retyped and crossed and transfused he had lost vision in one eye. That is how profound these kinds of diseases can be.

One of the things as I was thinking about that in the context of what we have heard over this time, I think that there are some things that we can think about, particularly for nano-rare diseases. One is the whole concept from which we evolved was one of compassionate and then towards either an accelerated approval or a traditional approval, and one of the things if we prospectively designed for let’s say protein S deficiency, we could create kind of a two-pronged approach for data collection. A scenario whereby

since these babies like protein C deficient show up almost instantly with purpura fulminans or blindness or whatever where a compassionate component could be interceded with where you could get legitimate -- if you did this prospectively, legitimate clinical data.

In addition then, I liked what Dr. Nugent said about with extremely rare diseases focusing then the pharmacokinetics and the more longitudinal data collection, and I would say that once those children survive those initial insults for which you gather very assiduously collected data then they would be referred -- the five in the United States, would be referred to one site with expertise in the pharmacokinetics of in this case protein S deficiency and get those during their steady state under good control with a replacement product, be it plasma or recombinant. Then that could serve as the basis for an accelerated licensure. Then in the post-marketing collection of the data one could put together the registry for these five patients and follow their life span along and continue to provide.

So again, just to be provocative I thought I would throw that out, and I think it is important because I think it focuses several of the -- what I have over these times been taking a few notes to try to say that I think are critical. Yesterday Dr. Lowser* talked about the phenotypic,

and we have heard other people talk about, the phenotypic variability. That is a real problem, and the rarer you get, the more the outliers are. I might tell you that that child -- I didn't quite finish the scenario, because that child did turn out to be homozygous S, and the mom was wrong about the father, or at least wouldn't admit to it. So that is the other caprice that I think invariably hits. The rarer you get, the more difficult it is to control for those caprices in data collection, and that is why I think we have to keep that in mind, particularly as we go from milli- to nano-rare diseases.

Then finally I am throwing all these out to the panelists and to the audience to just engender discussion. I think one of the things that could be utilized that has been utilized in the UK for instance -- and we obviously in the United States have to approach the Office of Human Research Protection about it, but they have for certain scenarios they have a nation IRB. And for really, really rare diseases where you could prospectively get an IRB approval you could not only potentially cut the cost which we heard about from Dr. Nugent, but in fact we could speed the whole process up by months or years. Since these rare diseases come along so rarely, one would then be able to at disparate sites around the United States be able to enroll children quickly. First

on the compassionate if need be, and then on to the broader prospective, single-site or multi-site data collection phase.

So with that, I am going to open it up for questions from the audience, which I think is the strategic part of this whole conference, and also for comments from panelists. Over here on my right.

DR. GUSTAFSON: Okay. Mary Gustafson. We will stay with recruitment. Yesterday we heard mixed messages pro and con on whether it is difficult to recruit or not recruit. I think Amy Shapiro mentioned the problems with compassionate use and being caught in an investigator IND situation. So I would like to ask any of the panelists, I know Dick Scotland mentioned problems with recruitment, are issues with recruitment centered around the number of patients, or do the bureaucratic procedures enter into that?

DR. HOOTS: Dr. Scotland? Both of you, one after the other.

DR. SCOTLAND: Okay. I will start off then. In terms of patient recruitment it is actually partially related to our ability to get patients in through the regulatory process in time. So for example if we identify a patient in a given country who might be eligible if we don’t have the regulatory process in place to be able to treat that patient, ship drug to the physician, we are not able to do that. The

same thing goes with the ethics committee. In terms of compassionate use, I should just make a comment that we have generated, collected some compassionate use data. We have made the drug available to physicians in the United States at a time when antithrombin was not available.

DR. HOOT: Dr. Gelmont.

DR. GELMONT: We involve all the patients that we knew of that had several protein C deficiency. Four patients dropped out. One baby died from unrelated -- from CNS disease not related to protein C deficiency. The other three dropped after a while because the burden of the protocol was inconvenient for them to come from where they lived to the center. They had to, some of them, travel 200 miles to the center. They didn't want to stay there. They had other life. To get all the information we wanted from that, so the burden of the protocol ended up in losing about three patients.

With regard to the phenotypes that you mentioned, the homogeneity of patients, that also created a problem for us. One, you know, there is type II protein C, and that is ultra, ultra rare or whatever you want to call that, and we had one subject with double heterozygous that was -- so we had some level, but not functioning level. So that screwed up the PK data.

DR. HOOTS: And I think that is very important and I think the more you go to the rare end of the spectrum the more you have to understand that the idiosyncracies of nature will probably impact you more commonly percentage-wise, just as you said, and you have to be almost prospectively prepared for that to happen. Not so much that you can group that data with homozygous quantitative deficiency, but in fact the data from that individual may be very important when you are only enrolling 12 patients or five patients. Yes, Dr. Nugent?

DR. NUGENT: I think that one of the issues also for recruitment of patients is that if you want to have a centralized approach and bring all the patients to your center then the onus is on you to get the information out there. You know, on the list serve, for us we used ASH, any organization that we thought we could reach physicians that might potentially be treating factor XIII deficient patients. All of those recruitment materials had to go through our IRB prior to putting them out, but that was just one time and it went well. The other side, when you are -- and, again, Jonathan is the one who said let’s just not give this out compassionately. Let’s set up a trial. Let’s go ahead and collect the data.

Once the Fibrogammin trial started then the patients sort of came to us. Any physician that made the

diagnosis went online and said is there a factor XIII product, contacted the company, and then the company sent the patient through to us. So there is kind of two different processes there; one is the -- but either one you are able to collect the data and on an ongoing basis. But going out there reaching and truly advertising, the result was actually a very effective system for us.

DR. HOOT: Dr. ---.

DR. : Yes. First a comment and a couple of questions. The first is if we are talking about replacement of a deficient enzyme that causes a disease or a protein it seems like you have a very plausible and obvious mechanism for the mechanism of action for your product. But if you are proposing let's say a therapy where you are not replacing that specific protein, it seems in that scenario you have a greater burden perhaps than otherwise to show clinical benefit empirically by whatever mechanism. So my question would be for the clinicians in the panel and the audience let's say with regard to something like Glanzmann's thrombasthenia where you have an issue where the natural history is quite varied let's say, and then you go in and test something, whether it is Novo VII or any other drug. What practical or ethical issues would there be with patients serving as their own control where you might be comparing use

of Novo VII or another product with either standard care, in combination, or to placebo in a situation that is not life threatening, but one that is serious but usually not life threatening, such as epistaxes or menorrhagia or something like that?

DR. HOOTS: Well, Dr. Rajkjaer, do you want to start with that since you were the who spoke about Glanzmann's?

DR. ROJKJAER: Sure. I think that is an excellent question and it is certainly something that we have been considering, just the point that you mentioned when -- as it is, you know, looked upon now as rescue therapy essentially in patients that develop antibodies to what is defined as being the effective therapy. I know initially in the observational study the patients that -- of the four patients, they were also looking at patients that were sort of geographically remote. You know, in areas where they couldn't easy match platelets, HLA matched or cross-matched platelets, and I think that is where we really need to enter into a discussion or a dialogue with our physician experts on this to see, you know, what are their attitudes towards enrolling patients in that type of study and the patients themselves given that there is some literature out there where people are aware that Nova VII is effective therapy.

But I don’t know if that completely answers it, but it is not something we can sort of decide on our own.

DR. HOOTS: Ms. Lawton.

MS. LAWTON: I just wanted to comment the very first product we got approved for actually for enzyme replacement therapy, I know you weren’t talking specifically about that, but for Gaucher disease the first product was actually a placental derived before we developed the recombinant. For that approval we used patients as their own control and showed historically their decline and then after treatment their improvement. I think depending on the disease though again is the heterogeneity and is there any likelihood of, you know, could they spontaneously not progress any further or -- I mean, that has been a big discussion that we have had around, again, how much historical data do you need to show that at the time you give them the treatment what you anticipate their onward decline would be if they hadn’t had treatment.

DR. HOOTS: Diane.

DR. NUGENT: The incidents of antibody in Glanzmann’s is not 100 percent with platelet exposure. SO I think that that adds another nuance to this because if it were that all patients became refractory with platelet exposure then one could easily argue that let’s use Novo VII

before that event and save the platelets for when you really have a huge life-threatening process. A little bit the way we do with factor VIII inhibitor patients where we get their -- we kind of get their titer down to zero and then you feel like you want to hold off on the VIII until unless you really need it. This is before we had bypassing therapy.

I think anything that can prevent the incidence of antibody development is critical important because we know that people that make antibody make anti-idiotypic antibody to that antibody, which results in antibody to fibrinogen, which at that pont becomes a life-threatening bleeding event that you cannot correct with platelets or Novo. So I think that they have nicely demonstrated that in patients that already have an inhibitor that Novo is useful. It will take involvement with I think an advisory team to decide what that next phase is. But, you know, how bad the bleeding should be I think is a result of an advisory committee saying what is the guideline, and doing that up front as everybody on this table has suggested to really think about what you want to be your clinical endpoints before you start the study will save so much time.

MR. : Just one quick followup is that we have a recurring theme in evaluating blood coagulation products. It is not to pull out the legal quotes too often,

but there was a jurist who said he couldn't define obscenity, but he knew it when he saw it, and that is the them I hear quite often with evaluations of hemostasis. So I would ask the people who are clinicians in the crowd here what they would consider a time line for effective hemostasis. Let's say in the platelet disorder, because there have been quite a few experts who have had different opinions about that; and I don't know that we are gong to solve that here, but it would be interesting to hear what people thought would be a reasonable time to declare success or failure.

DR. NUGENT: I think that is my point, that you get an advisory committee together and you define what that is for your study. You will never be able to get an agreement on that in a huge arena, but to say for platelets specifically what kind of bleeding, how long bleeding, you know, what are your indications. It would be another hour discussion probably among haematologists to define that, but you are exactly right. That is what you need to do prior to entering in on that study.

DR. HOOTS: And I might just add as a caveat sometimes you have to take other licensed drugs into consideration. The perfect paradigm would be if you were talking Epitaxes to get hemostasis and then to start anti-fibrinolytics so that you don't get into the compounding

effect of secondary bleeding versus not really having stopped. I think those kinds of things are where advisory committees are essential to try to say what is permitted, how it is to be used, and make sure that it is used consistently. I agree with Diane 100 percent on that. Yes, question here.

MR. : ---, University of California. I think that I just want to make a point to Dr. Lawton's suggestion that the blood products advisory committee of which I was a member in the late '80s and early '90s serves as advisory to FDA and could not serve in fact in its own structure --- the Blood Products Advisory Committee could not serve as a consultant to the industry at the time in which you intend that it would be nice to have a dialogue and so forth. But that is precluded from that possibility because that is not reason to have the Blood Products Advisory Committee. It is an advisory committee, and advisory only to FDA.

MS. LAWTON: Could I just make a comment on that?

DR. HOOTS: Yes, Ms. Lawton.

MS. LAWTON: From our experience with these very rare diseases normally the experts for these very rare diseases do not routinely sit on advisory committees because for example with us, the Endocrine Advisory Committee, they did not have experts sitting routinely there ready to talk

about Gaucher disease or Fabry disease or MPS-1. So of course FDA have to bring in special employees who have the expertise to review those very specific diseases. That is when you have an issue because we as the sponsors are working with those experts during the clinical development program and then the FDA is trying to find experts who they can bring in who are still independent to give them advice. So it is a slightly different situation. I understand completely when you are an SG and you are on the advisory committee all the time, but in these cases, in these cases of rare diseases, you go out and look for those experts when you have that particular topic. At that point sometimes they are really tough to find.

DR. HOOTS: Yes, Dr. Gelmont.

DR. GELMONT: In the European community there is a scientific advice tool where the company can come and get scientific advice with regard to any kind of drug. Now it doesn't make the authorities adhere to the conclusions of that committee, but -- scientific advice, but it really helps in coming to agreement with authorities to what kind of clinical development we should have. If the FDA have something like that as in independent people who are expert in the field and willing to serve on that, that would be very helpful.

DR. HOOT: Another comment?

MS. LAWTON: Yes, just one more comment. I think I will mention that in many meetings we had with the FDA in the process of getting Fabrazyme approved we brought experts that we had been working with, and I have to say these were real leading experts in that field. I think the FDA were very open to listening to them and hearing their perspective even though they were there, you know, the sponsor brought them. I think that still is a very important piece, an opportunity to learn from those experts.

DR. HOOT: Good point. Another question? Yes, last question. We are going to have to close because we are behind schedule.

DR. WALTON: Are you pointing to me? Paul Walton, ZLB Behring. This is for Diane Nugent. A great presentation, I really did enjoy it. A comment and a question I guess. One thing I noted from your presentation was you raised the point about dealing with three companies with respect to the plasma-derived factor XIII. Just a point of correction. It may be trivial. It was in fact one company which changed its name during the time period that you spoke about and made a merger, but in fact, you know, the stability of the organization didn't change. It wasn't really three organizations. I know that in the plasma

business these sort of changes have been -- occurred lately. The question I had for you was I also noted you didn't tell us who the manufacturer or producer of the recombinant factor XIII was, and I wonder if you can do that now.

DR. NUGENT: Thank you. Actually that was it is changed now. I did put it on my slide, so the slide show that is available online for everybody includes it. The company that worked with in the initial phase I trial, the PK and dose finding, was a company called ZymoGenetics. It is in Seattle. Earl Davies originally founded it, and an excellent company, phenomenal company to work with, and after that first trial was completed the subsequent trials now on a much larger scale are going to be done by Novo Nordisk. I did neglect to put those names on the slide, and I thank you for pointing that out. I will say that with three company changes, however, it did not seem like one company.

(Laughter.)

DR. NUGENT: Number one, and number two, it did require us changing on the IRBs. We had to make a modification, and every time a vial size changed, which also changed with the companies, then we needed to make that. So let me say that I appreciate support all along from the company, although by whatever name was there. But believe me, although it may have been one company, there was

definitely a different phenotype with each change.

(Laughter.)

DR. HOOTS: We can go just a little longer, and then we will end by noon. Jonathan?

DR. GOLDSMITH: I think we heard a lot of different views of review of literature and going back and reading charts to get additional information about a lot of these rare protein disorders. Do you have any advice about how to make this a more robust process, a way to go back and use the literature in a more effective way to learn more about the natural history of these rare diseases? Lots of you mentioned this, so the question is to everyone.

DR. SCOTLAND: Maybe I can that to start out with. We actually did try to use the literature to support historical control, comparator arm, and that was deemed to be adequate. So that is the purpose and that is the reason that we are now going back through medical charts. We do recognize that there are limitations as to what you can actually extract out of those, out of the literature on individual cases. So in order to have a matched comparator we are really limited by the use of the literature, regardless of whether or not you do it with an evidence-based practice center or not.

DR. GOLDSMITH: Could you go back to the original

source documents that were used for these articles? Could you go to the investigative sites and look for the raw data?

DR. SCOTLAND: That is a possibility. However, I think as Dr. Lauchenbruch pointed out yesterday, there is an issue with regard to contemporaneous data versus older data, and that becomes a problem. I think at that point there becomes an issue of whether or not that is even worth it as opposed to just going out and doing a more rigorous historical study. We actual go in and extract information out of medical charts.

DR. HOOTS: Dr. Rossi.

DR. ROSSI: Yes. We do use published experience, and of course you do have to look at it with a critical angle and just to order whatever is available. For our --- antitrypsin in the literature there was an article with our own product, and whenever your own product is in the article then it is very much supportive data with the limitations of no monitoring or descriptions which are not as a clinical study. But we were actually able to go back to the patient files and documentation and to remonitor in a way and do a statistical analysis on the published literature. So it can be very useful, but again you have to look at it with prudence I would say.

DR. GELMONT: Well, our experience is not as good

as LFB obviously. They had a very good study done in data marketing in ---. But I can tell on top of all the issues of time elapsed and different endpoints and what -- some investigators published the same patients in more than one article, and it is very difficult and very complicated to view the literature in a really critical way. It took us a long, long time, and we got only minimum information. We want to know, for example, how long does it take for the effect of protein C compared to other treatment, and there is no data whatsoever. You can't tell. You can't tell about dosing of fresh-frozen plasma or any other product that we used at that time, so it was very, very limited. We learned something, but we cannot learn a lot. We learned something about adverse events, but not much more than that.

DR. HOOTS: Yes, Dr. Gustafson.

DR. GUSTAFSON: This is more of a comment than a question actually, and yesterday and today there were several presentations that talked about the inherent risk of human source material. But Juan Jorquera had in his presentation something that I think is worth mentioning. He showed the current pathogen clearance methodologies and final therapy manufacture, and those advances coupled with the careful selection of donors and testing of donors and adherence to government requirements and voluntary standards have made

human source material very safe today.

DR. HOOTS: Thank you for that comment because I think that is obviously a requisite for all the stuff we have talked about, and I think that is one -- it is because I think we believe what you said and you believe what you have just said, too, that we are able to spend all our time talking about how to measure efficacy, and I think that is still critical. We can never drop the vigilance on that one. That is the most important thing. Are there any last questions before we close this session and move on? Thank you very much to the panelists for excellent presentations and discussion. Thank you.

(Applause.)

Future Opportunities - Enhanced Data Collection

Nisha Jain, MD, Session Chair

DR. JAIN: We are running behind schedule, but this section is devoted to the post-marketing data collection, and in this session before lunch we will hear FDA's experience, the ICH pharmaco-vigilance planning, and the EMEA experience with the post-licensure data collection. The first speaker for this session is Dr. Ross Pierce, and his topic will be -- is actually, FDA Experience with Post-Licensure Data Collection.

FDA Experience with Post-Licensure Data Collection

Ross Pierce, MD

DR. PIERCE: Can you hear me okay? Thank you very much for the opportunity to speak with you today. There is a new handout. My talk has been slightly revised. The new handout is out front, so if you want to follow along with the old handout it has the small slides rather than the big ones, just remove page four if you will and pass that to your left and we will collect page four at the end. I am going to give you the standard disclaimer that my remarks don't necessarily reflect the views of the FDA, or even my own for that matter.

(Laughter.)

And I want to mention that some of the data that I will be presenting, some of it comes from the FDA website, some of it does not, and some of the data therefore is preliminary in nature, might contain errors and has not been independently validated.

(Slide.)

So what is definition of post-marketing study commitments? It is studies required to or agreed by FDA and a sponsor conducted after FDA has approved a product for marketing. These are used to gather addition information about a products safety, efficacy, or optimal use.

(Slide.)

It is important to recognize that agreements for

conducting post-marketing studies can be entered into either before or after FDA has granted approval to the sponsor to market a new product.

(Slide.)

Now the authority for monitoring and reporting of post-marketing commitments was updated by what we call FDAMA, the Food and Drug Administration Modernization Act of 1997, which added a new section which provided for the monitoring of the progress of post-marketing studies for both drugs and biologics.

(Slide.)

The impetus for that legislation was basically in response to concerns that had been expressed by the FDA and by the public about the timeliness up through the mid ‘90s of completion of post-marketing studies and the need to update drug labeling within the information retained from those studies. There also was a May, 1996, Office of Inspector General report that highlighted a number of concerns with respect to the timeliness of conduct of post-marketing studies and what was done with that information after the studies were complete.

(Slide.)

The new provision for FDAMA required that sponsors of approved drugs and biologics report to FDA annually on the

progress of their post-marketing commitments, and in addition FDA is to publish annually in the Federal Register a report that provides information on the status of post-marketing studies that sponsors have agreed to conduct and for which annual reports have been submitted.

(Slide.)

FDA also agreed to make basic information about the status of each post-marketing commitment available to the public on the internet; and in your handout you will see the URL, and I would encourage you to actually look and do a little browse of the FDA website relating to post-marketing study commitments. You can actually do searches on various criteria.

(Slide.)

The information that is currently available to search include both the commitments made by CBER at any time and those post-marketing commitments made with the Center for Drugs since January, 1991. It is important to emphasize that only those commitments which have been reviewed for accuracy are included in the current online list, and the list is updated quarterly. So when I looked through the list for the post-marketing commitments online available to the public for biologics or from Center for Biologics, I noted that at least one was missing, and the number of post-marketing commitments

which I was able to identify, which was about 66, was less than what is mentioned in some of the statistics that I will present. So that suggests that some of the other post-marketing commitments haven't yet been able to completely checked for accuracy, and that is maybe why they are not yet on the web.

(Slide.)

One you browse the website relating to post-marketing commitments, if you have questions or comments you can send them to this Post-marketing Study Commitment Coordinator at that web address that you see there.

(Slide.)

This is the URL for accessing the post-marketing commitment study status for both CDEER and CBER.

(Slide.)

There also is a draft guidance which is available at the URL listed at the bottom of this slide that instructs industry on how they may structure their reports on status of post-marketing studies in order to be compliant with FDAMA.

(Slide.)

There also is a report to Congress which I would -- or webpage or section of webpages that I would encourage you to examine, and the URL for that is listed right here. It goes into some of the history of post-marketing commitment

tracking.

(Slide.)

Now various factors may delay the initiation of post-marketing commitment studies. As of February of 2002, according to that URL that I just listed, 44 or 301 post-marketing commitments for biologics had been completed, and 882 out of 2,400 PMC commitments for drugs had been completed as of 2002.

(Slide.)

A recent Reuters news release, which has not been independently verified by FDA, about citing, nevertheless, FDA data claimed that46 percent of 91 studies started since 1992 specifically of drugs that had received accelerated approval were incomplete. The article quoted that "Companies have been selling these products to the public for an average of one-year-and-10-months and up to six-years-and-nine-months without initiating the required studies," according to the report. If you do browse the FDA website for post-marketing studies for CBER you will find, you know, one or two instances of post-marketing commitments that are still ongoing after about ten years or so, or at least 10 years since approval.

(Slide.)

In 2003, published figures showed 349 studies for

chemical-based drugs were completed, while 61 percent of 1,339 outstanding studies had not yet been started. This was again from the Reuters article. An informal June, 2005, analysis that I performed, which again has not been independently verified, using the data publicly available from the CBER website, from the FDA website but limited to biologics, showed that 20 percent of 66 CBER PMC's, post-marketing commitments, had been fulfilled or released; 12 percent had been submitted; eight percent had been termed delayed; 21 percent were not initiated, and the terminology there is pending; and 39 percent were ongoing.

As I mentioned, I was able to locate at least one old post-marketing commitment did not appear on the website. So we can ask the questions will improvements that have been ongoing in FDA's tracking system for post-marketing commitments help assure more timely completion and reporting of PMC study results. One of the problems that we have with the information available online is that in the case of at least the PMCs listed in the biologics part the minority of them show a planned -- an original planned completion date for fulfillment of the post-marketing commitment. So it is difficult in many instances for an outsider to assess the progress of the fulfillment of the post-marketing commitment in terms of whether the study is really on track or not. It

is possible to see if it is not yet initiated because then the database will say pending, but if the study were originally -- if it was originally envisaged that the study would complete in 2006 and you are in 2009, you can't necessarily in every case tell that from the database the way it is presently executed.

So FDA does have some remedies in the extreme cases where an applicant would fail to complete required post-marketing studies under accelerated approval. These remedies are not available to us for post-marketing commitments that are entered into for regular approval. You know, not accelerated approval.

(Slide.)

Those remedies are failure to complete studies under accelerated approval may result in the withdrawal of approval, withdrawing of the drug from the market, or modification to labeling claims. Also if there is a failure to execute and submit required pediatric studies that are deferred into the post-marketing time frame it is possible that the FDA deemed the product to be misbranded and in theory FDA could initiate seizure or injunction actions. I am not aware of any instances where the first example here has actually taken place, nor of the second, but I am more familiar with the first.

(Slide.)

So there are other types of problems that can occur with the execution of post-marketing commitment studies. There was an instance in which the European authority, the EMEA, rejected a post-marketing study after it was complete based on good clinical practice deficiencies that came to light during European audits. Also there can be design problems in post-marketing studies, and a lack of blinding in at least one randomized clinical trial that was a post-marketing commitment lead to grossly unequal dropout rate in the treated and untreated patient groups, invalidating the study conclusion that the test product was harmful compared to no treatment at all.

(Slide.)

So if look at what lessons we can learn from the post-marketing experience of FDA so far I think we can say that we have had a lot of positive instances where post-marketing studies have been completed and have offered valuable additional data regarding efficacy and/or safety of products that have received either regular or accelerated approval. We know that post-marketing commitment studies can help to further validate surrogate endpoints when there is room for additional validation at the time of product approval, and there would appear to be room for improvement

in the timeliness of post-marketing commitment study initiation and completion in many instances. I would also add that when trying to interpret in any given instance whether a sponsor is on track or behind schedule, it should be noted that sometimes it can take up to a year or so to actually negotiate the design of a post-marketing study, and the final protocol design is not necessarily finalized as of the time that the post-marketing commitment agreement is entered into. So that concludes my presentation, and were there any questions?

(Applause.)

DR. JAIN: I think we have time for one question. Diane.

DR. NUGENT: This is becoming of course more and more of a focus, and for those of us who are doing chemical trials for products, biological or other drugs, are really finally beginning to get the post-marketing aspects of the data collection. But it struck me that with the other speakers in the last two days they will say we did post-marketing looking for an inhibitor, or we did post-marketing looking for one or the other things. One would not have predicted eye problems with Viagra. I think that we could improve what we look for in our post-marketing by keeping it as broad as possible. One of the things that we have thought

of doing is just having on an annual basis because these diseases are so rare to actually either do teleconferencing directly with the patient or getting somehow one-on-one with the patient on an annual basis to look at all possible things and see whether they relate or not.

What are you doing about defining the specifics of what you look for in a post-marketing study? Whose job is it to define what we look for?

DR. PIERCE: I think that is an excellent question, and as you point out the situations in which the patient population is small affords a unique opportunities to do more extensive, you know, followup if there is perceived to be a need for that. But in the post-marketing study database for CBER that I went through, it really ranged the gambit in terms of in some cases you were looking for very specific information and in other cases it was very broad just to gather additional safety on the use of the drug. So I think there is an opportunity for tailoring post-marketing studies to the individual situation, but of course there is a lot of talk these days in general about how we all can gather, you know, information more efficiently with respect to safety for example.

DR. JAIN: Okay. Our next speaker is Dr. Miles Braun from the Office of Biostatistics and Epidemiology, and

his topic is FDA experience work -- expert working group for ICH E2E pharmaco-vigilance planning.

(Adjusting equipment.)

FDA Expert working Group for

ICH E2E Pharmaco-vigilance Planning

Miles Braun, MD

DR. BRAUN: Hi. Thanks. I appreciate the invitation to talk today. I am going to actually talk about three guidances, so it will be a three-for-one in my short talk. But I won't go into details on the two guidances in addition to the ICH pharmaco-vigilance planning, but I think these other two guidances are relevant. I provided handouts that give you the highlights of all three guidances that really try to be useful reference guides to what may sometimes be dense guidance documents that we have at FDA, and they are even denser to try to write. I was involved in writing two of them, so I can say that first hand. So what I will do is I am going to go quickly through two documents and then focus on the ICH, International Conference on Harmonization pharmaco-vigilance planning guidance.

(Slide.)

As probably many of you know, guidances are an iterative process and they differ from rules in that they are non-binding, and so alternative approaches are allowed.

(Slide.)

As I said, I am going to go quickly. I have a lot of slides. This first guidance is one that we published this spring. It deals with pharmaco-vigilance practices and pharmaco-epidemiologic assessment. You have the web link there and you can have all the detail you want.

(Slide.)

It is all there, so I am going to skip over.

(Slide.)

I just want to say that a safety signal as we define it in that document, you will hear that term a lot, and it is defined as a concern about an excess of adverse events compared to what would be expected. Signals generally indicate the need for further investigation, and it should be further assessed. Now I think the key word I want to highlight here is concerned. There is not a mathematically definition of what a signal is. A concern suggests that you need to imply medical or biologic thinking. There is judgement involved and it requires close scrutiny of the data.

(Slide.)

Signals don’t usually appear like this.

(Slide.)

Sometimes frequently and more often you get signals

like this.

(Laughter.)

And you don’t know, and I think those of us who do this kind of work have experienced that firsthand and that is the challenge.

(Slide.)

Good reporting practices outlined in the FDA guidance. I am not going through it.

(Slide.)

As well as the elements of a good case report. It is in there for your reference.

(Slide.)

I will point out something that is a little counter-intuitive I think, and generally the individual case causality assessments, even though they are involved in licensure applications, generally are not highly useful in an overall assessment of whether a product is associated with an adverse event. You need to bring in comparison groups and you need to bring in multiple individuals. There are exceptions to that, but this is really -- and it is in as well Center for Drugs, has a guidance that talks about this, although I can’t reference. I was reading it just yesterday, and they are of the same view.

(Slide.)

So it is a big counter-intuitive, but we need to bring into account population thinking and groups of patients to make inferences.

(Slide.)

I am going to skip over the importance of time to onset, which is a key issue in making causal associations between products and adverse events as well as re-challenge. That is occurrence of an adverse event when a product is given again.

(Slide.)

I will make one other general comment that I think is not widely appreciated, even by our leading medical journals, that reporting rates were the number of spontaneous reports, that is passive surveillance reports -- for example for MedWatch system, divided by the number of patients treated in a given time period. Those are not incidence rates, and the difference is that we have under-reporting with these passive surveillance reporting rates, and also it often very hard to obtain the number of patients treated or the denominator. So I just want to point that out to you because it is commonly misunderstood.

(Slide.)

A lot of times we are on a fishing expedition with safety data.

(Slide.)

Data mining is really the epitome of a fishing expedition. It is kind of a buzz word today, and it is discussed in our guidance beyond the scope of today's talk, but you are welcome to look at it there or in your handout.

(Slide.)

Your handout can be a bridge of going to the guidance. You can just look up some of these things if they are of interest.

(Slide.)

So I am going to now go into fast-forward and go to the ICH E2E pharmaco-vigilance planning document. I was involved with the group that wrote this; and, as it says, industry and regulators have identified need for better and earlier planning of pharmaco-vigilance before a license is granted. It could be after though. Knowledge changes over time. We all know that, and the idea is to feed back the knowledge to the users and the providers to improve the risk benefit balance.

(Slide.)

The main focus of the guidance is on the plan submitted at the time of licensure and it is intended for the products that we are talking about today. It would be appropriate. That is why I was invited. So this can be part

of a license application. This is new really. You know, so the common technical document that is the core of that application through the ICH process allows for this in the sense I should say that this is compatible with a common technical document.

(Slide.)

Pharmaco-vigilance, though, can occur throughout the life cycle. You can have signals at any time in the product's life. Obviously it is science-based as FDA is a science-based agency, and we collaborate with the industry in developing these pharmaco-vigilance plans. They apply across the three ICH regions which are the United States, Europe, and Japan, and increasingly other areas of the world are paying attention. Someone in my group representing us at a Paho* meeting in Guatemala, and this was a lot of interest in this document there from Central American/Latin American countries.

(Slide.)

This document has three sections: safety specification, pharmaco-vigilance plan, and the annex is I guess a British way to say appendix.

(Slide.)

ICH safety specification, now this is a key part of it. It can be standalone. Now some of these portions of the

safety specification which is like a safety inventory, are found in the common technical document or the other part of the as I said the core of the application. But we have been asking when we have asked for these documents to have the standalone document because it makes it easier for us to review, and you can reference material in the common technical document. But again ideally it would be standalone. It really helps the review.

(Slide.)

This safety specification or inventory would talk about non-clinical material, and it is outlined here. This could be laboratory or animal data.

(Slide.)

Then the clinical data is really important, and I think for the products we are talking about in this meeting, the size of the study population is a major limitation from the sense of trying to detect rare or even not so rare adverse events. So it is something that needs to be discussed about what the implications of the small study sizes are prior to licensure, and exclusions and inclusions are always important I think in our safety evaluations. We will talk more about that in our next slide or two, and what the implications of these limitations or exclusions are. If there is experience from other parts of the world that should

be reviewed here if the US is not the first country to see this product or to have it evaluated.

(Slide.)

So here are some of the classic populations that are not studied. Frequently studies will exclude children or the very old. Pregnant women are another common group excluded, people with HIV infection. You know, there are many, many of them, and they are listed here. So this may have implications in the post-licensure period when sometimes these groups will receive the products and needs to be described.

(Slide.)

So the most important that we now we are talking about focusing in on some of the more important adverse reactions, and to go through these specifically to describe evidence bearing on causality, and those are readily available criteria. There are some variations in the ones used, but they are pretty standard, first described by Bradford Hill. So those are gone through, and then the severity of the adverse event can be discussed and how frequent it is. So a basic, again, inventory now focused on the actual adverse event itself of interest, and there may be multiple.

(Slide.)

Now drug interactions between food and drugs or drugs and drugs are important to describe, and any other risks that need further evaluation. What we are talking about with epidemiology of the indication, if you are studying a rare disease frequently there are other medical conditions that occur in addition to that disease, perhaps as a result of it. So it is helpful to describe these prior to licensure so that these other manifestations of the disease are not misinterpreted or otherwise confuse the assessment of adverse events. Similarly the epidemiology of the adverse event itself ought to be described to outline and to prevent a misunderstanding about whether this population will be more or less effected by this particular adverse event. Finally, there are class effects. If there is a product in this class that has already been describe to have an issue then you need to discuss it for your product.

(Slide.)

So thus we have gone through the assessment and the inventory, the safety specification, and now we summarize it and move on to what is the plan.

(Slide.)

What are the issues, and the first thing is what is your routine practice. Now in dealing with large pharmaceutical manufacturers, you know, the Pfizers, the

Mercks, they tend to have well-oiled machines. Sometimes with smaller companies basic routine practices may not be as well-oiled machines, and so it is important to describe what the routine practices are. I think our FDA guidance that I already discussed before going to the E2E document is a good place to start for people or groups that are less familiar with routine pharmaco-vigilance.

(Slide.)

That done, then we focus on the safety issue and what is the proposed action that you are going to implement to monitor this issue and to learn more about it. You need to describe the -- state the issue, say what the objective is and then say what the action is, why that is important, and how you are going to oversee this study or this other way that you are going to gather information and perform pharmaco-vigilance for this issue. As was discussed by my prior speaker, there has been some slippage of time lines. So now we are asking, you know, for these milestones up front.

(Slide.)

So a protocol would be developed with, at a minimum, aims and objectives and the methods, just like any protocol would; and there are ISPE, International Society for Pharmaco-Epidemiology guidelines on how to do pharmaco-

vigilance studies or pharmaco-epidemiologic studies and these protocols.

(Slide.)

Finally, for those of you who are less again familiar with this area, a lot of the terminology is described in this appendix or annex, and you can look it up. These are some of the headings here that if these terms are not familiar to you, you can look those up in the annex of this document.

(Slide.)

So that is the E2E guidance, and now the FDA also published a guidance on development and use of risk minimization action plans.

(Slide.)

In this guidance here are the goals to minimize risk, maximize benefits, and you have one or more safety-related goals.

(Slide.)

Here is an example. Patients on drug X shouldn’t be prescribed drug Y; or another one, another goal, would be fetal exposures to drug Z should not occur.

(Slide.)

So you set up a goal like that, and then, you know, there will be a process of whether you need to actually have

a risk minimization action plan, and these are some of the consideration. Whether it is preventable is a really important one, and again kind of obvious, but sometimes --.

(Slide.)

I will just take a step back and say this is an area of a lot of interest at FDA and we realize that it is not a science that is certain like physics. There is a lot of experimentation and learning going on on how to best do this. There are three levels of tool categories, from the least invasive if you would, the least burdensome to the more elaborate performance-linked access systems. I am not going to go into the whole scope of this. Again, it is laid out in my slides which you have for reference, and I am actually going to stop now. If there is a question or two I can address it, and again this is meant to be a user-friendly document that I have provided you.

(Applause.)

DR. SCOTLAND: Yes. Dick Scotland. On the risk minimization plan, could you tell me, has there been a pilot program for this and are there any lessons learned from that? It seems to me that for these rare diseases to add this additional level or burden on top of what is already asked of us is going to be a real challenge. If we can it as efficiently as possible that could help reduce the angst that

perhaps I have about this.

DR. BRAUN: Right. Well, that is a good question, and I think the first thing to say about that is they are not intended to be implemented on every new product. So it is on a case-by-case basis. Okay? So when they are indicated and there are a lot of specifics then we go into that decision. So that should give you some reassurance. But this guidance document is intended to just create a template so that should you -- should one of these plans be indicated it will give you guidance on how to develop it. It has been piloted in the sense that a lot of risk minimization action efforts have been underway for different products with differing success, and it has not bee a formal pilot, but I think there have been lessons learned. For example, we know that the label by itself is probably insufficient as a simple example.

DR. SCOTLAND: If I could just followup on one additional question, and that is the data that is actually captured in these plans is actually entered into the adverse event reporting database that you have now?

DR. BRAUN: Well, it depends on what the data are. Okay. So if the data relate to adverse events they probably ought to be entered into such a database, but some of the evaluation if you read the slides, an evaluation is built into the risk minimization action plan. Some of them just

are process measures and don't deal with adverse events directly, so those would not go into an adverse event database.

DR. JAIN: Do you have a question?

MR. : Yeah. I thank you for a very nice discussion of sort of the role of pharmaco-vigilance, and I think while the path to pharmaco-vigilance has occasionally proved to be very valuable, I think you have pointed out some of the difficulties. In the last day-and-a-half we have learned a lot about the use of say a more active pharmaco-vigilance system as an alternative to a formal clinical study, especially in a confirmatory setting for some of these very rare diseases and --

DR. BRAUN: I am sorry. As an alternative to what?

MR. : To a formal prospective clinical study, especially for confirmatory data collection in these very rare diseases where you need a patients followed for a very long time looking for safety issues primarily. I was wondering if you could comment on sort of what you view the role of active pharmaco-vigilance might be in these kinds of diseases that we have been discussing.

DR. BRAUN: I think you in your question you made a good argument for it. I think we would have to -- you know, the diseases being discussed here are atypical from, you

know, the vast majority of patients treated, so the patient populations are different. I think we look forward to working with the sponsors to come up with reasonable plans, and as I said it is a new area of research and development and implementation, and I think it is an iterative process and a collaborative process. I think added followup or more intensive followup certainly seems reasonable in certain situations, but it would depend on the particular instance. But I think that is the direction we are going, is for more safety surveillance, just as a broad generalization.

Now back to the hypothetical situation. You know, we would really have to look at the specifics, but that general rule could certainly apply in that case, and we are open to doing it. We are working right now with vaccines we are implementing, and of course these vaccines are ver different from these products, but we are implementing ICH E2E processes.

DR. JAIN: Can we ---? Okay. Thank you. Our next speaker is going to be Dr. Rainer Seitz, and he is going to tell us about the EMEA experience with post-licensure data collection.

EMEA Experience with Post-Licensure Data Collection

Rainer Seitz, MD

DR. SEITZ: Yes, thank you very much. With this

conference it is my fate to be the last speaker before lunch.

(Laughter.)

But I can assure you I am a very experienced last speaker, and I will try to be as short as possible. Okay.

(Slide.)

I start with a slide I showed you already yesterday. We are talking about very rare products and probably licensing under exceptional circumstances in the EU, and this licensing may be combined with specific certain applications, and these again my implicate post-marketing things.

(Slide.)

So if we have a very rare disease and we have limited data for licensing, then of course we are interested to get as much information about the patients and as comprehensive as possible information in the post-marketing period. This can be the usual pharmaco-vigilance system, and Dr. Braun told you very nicely about pharmaco-vigilance. I think this is quite similar in the ---, the principles of pharmaco-vigilance. Then there might be other information from the marketing authorization holder, and finally registries and I will come back to that.

(Slide.)

First of all, pharmaco-vigilance legislation is of

course a little bit different in the European Union, but I do not want to go into the details here. You can find the text, the legal texts which contain the provisions. The core of pharmaco-vigilance is that there has to be a person which is responsible for pharmaco-vigilance, and this person has to establish and maintain a database. That is really the personal responsibility of this person, has to prepare expedited reports in certain cases and the so-called PSURs. The are the periodic safety update reports. I will show you in a moment. And also to respond to any other requests for additional information, and particularly to the authorities.

(Slide.)

What is a periodic safety update report? It has to be submitted by the company every time the authority asked for it, but also on the periodic. That is the name, periodic basis. That means six monthly for the first two years after the marketing authorization, after licensing, and then annually for the next two years. That at the time of the renewal, and then at five yearly intervals afterwards. So these reports would accompany a product for its whole life.

(Slide.)

And these provisions are even increased being effective from November this year after a review of the European legislation. Then you will have to submit the

reports six monthly for the first two years as it was, then annually for the next two years, then three yearly intervals afterwards.

(Slide.)

There are a few other important developments. In Europe you have now computers and you can submit electronic reporting of individual case study reports. I hope that makes it easier for all parties. Then the change of PSUR cycle as I already told you, then of course the ICH guideline which was nicely explained already. I can skip that and the risk management plan, and there may be now penalties when pharmaco-vigilance obligations are not met and that is a new and special thing. This shows you how important pharmaco-vigilance is now taken in Europe.

(Slide.)

Then I told you there may be other information from the marketing authorization holder required. That can be data from specific obligations from follow-up measures. It can perform clinical trials in the post-marketing phase, or pharmaco-epidemiologic studies.

(Slide.)

We have an example for that, and we heard also today about Ceprotin. The company made some commitments when licensing the product. I think I do not have to go into

details here.

(Slide.)

How about pharmaco-epidemiologic studies? The typical ones would be cohort studies, which are very good evidence level. However, they need long observation times and large patient cohorts. There could be case control studies which would be retrospective, but also not easy to do, and we think that such studies are difficult to apply for rare protein deficiencies.

(Slide.)

Coming back to the subject of this meeting, rare protein deficiencies, this I showed you already yesterday. If the function of the lacking protein is well defined and symptoms are well established, then the clinical profile of the concentrate would be in principle predictable. Also the criteria of efficacy should be assessable, relatively readily because we have severe symptoms. You should find out whether the product is effective. The problem is more the adverse events, but also in this case we have some things, some deliberations which make it a little bit easier. We think the hazzard of pathogen transmission can be addressed nowadays not by clinical studies, but by scrutinizing the manufacture, the sourcing of materials and the validation and manufacture steps, and the clinical evaluation can really

focus on specific problems such as immunogenicity.

(Slide.)

Here is also a case study for illustrating this. Of course as we heard today, hemophilia A is by no means a very rare, super or hyper, or whatever rare disease, but it is a good example problems which you may encounter. There are two aspects. First of all, in hemophilia A it is conclusively shown that enhanced incidence or unusual type of inhibitor maybe product related. These were plasma-derived products in Europe which had to go from the market, and when we tried to scrutinize the pharmaco-vigilance data we found out that the information collected is quite heterogeneous and there are several definitions critical. For instance, what is a previously treated patient. You know that at least in Europe they are focusing on previously treated patients for finding out product-related immunogenicity and so on.

(Slide.)

Just to give a flavor of the problems, when the two clusters of inhibitors with the plasma products turned out I turned you before it was around 1995. We asked all the companies do you have reports of PTP inhibitors, previous-treated patient inhibitors, and the answer was "No. We do not know something like that. That is extremely remote," and so on. Then in the period between 2000 and 2003, maybe due

to increased awareness to this problem, we received reports, and in the case of the plasma product it was 10 reports and in the case of the recombinant products it was 62 reports. The number of reports you heard already from Dr. Braun. Of course as a regulator you have always in mind that recombinant products may show some small differences compared to plasma factors, e.g., post-translational processing differences like glycosylation and so on, and there is of course a concern of enhanced immunogenicity.

(Slide.)

However, what is the problem? You have already heard the number of reports is not the same as the incidents of the side effects. Possibly we had different vigilance and motivation to report concerning old products and the new recombinant products. Also we found out and it is really amazing what we found, the quality of documentation and presentation of patient characteristics is very different. Sometimes you get almost reliable information if you try to scrutinize a single case. Also the laboratory assessment of inhibitors is a problem. The test methods used are very different; and I remember two years ago there was a workshop about inhibitors, and Sandra --- from the NRBSC told us about quality control collaborative study in the UK where the values were so different you can really also use the dice and

try to find any numbers by using cards or something like that. Then also the assessment of inhibitor characteristics, for instance type I or type II. Most of the colleagues don't know what it is, but in the clusters we found in Europe these were so-called type II inhibitors with an altered dose response pattern and altered kinetics. Also the clinical significance, just to find out it was a clinically-significant inhibitor or not is sometimes difficult, whether it was transient or not, and so on. Even the definition of patient groups is different. What is a PUP, what is a minimally-treated patient, what is a PTP, and so on and so on.

(Slide.)

So there are a lot of things to discuss, and our colleagues from the pharmaco-vigilance division tried to scrutinize the data.

(Slide.)

They did not come very far. Of course I cannot give you very much details of that because many of that is confidential. But the observation from the spontaneous reports about PTP range from one inhibitor per 78 million units used to one inhibitor per 7.4 million units used, and the overall incidence in studies, in post-marketing studies, ranged from zero percent to 2.2 percent. You have always to

remember that some years only a few years ago we got the answer that is something you do not find, rarely.

(Slide.)

So the conclusion of our colleagues was that the available data seemed to be different and the design of the reviewed post-marketing studies was not only solely observational, but there is also a severe lack of consistency of the study design and the definitions applied.

(Slide.)

Therefore, there is really a need to come to better definitions and to scrutinized the assays used, as we had already said, and predefined and uniformly applicable requirements and standards for performing valid post-marketing studies are clearly and urgently needed.

(Slide.)

My last point, another very objective thing would be registries because registries in principle would really be promising because they could provide an opportunity to collect relevant information about most, or even all if we are lucky, patients with a rare deficiency. It would be a possibility to follow standardized rules and accepted definitions. It would cover all relevant parameters. It would also enable evaluations which lead to comparable data and not what I showed you before, and of course this is also

very attractive also for the scientific community. Such registries would be a very good tool for further scientific evaluations of what we are doing with the hemophilia patients.

(Slide.)

However, also registries are not easy to do. Lots of things which should be -- which need to be present in order to be successful. The first and most important thing I think is the support and input from patients and treating physicians. Of course at the end, we are working for the safety of patients, so it should be possible to convince the patients that it is important to take part in things like that. We need also to talk with physicians. Our experience with physicians is it is not so easy to take them all into one boat. To have 10 hemophilia treaters in one boat may even be dangerous.

(Laughter.)

Then we need consensus about the objectives of the registry, what is important that we want to have, what do we want to do with this; and also a very important point is an independent control of the registry, independent management and funding. At least in Germany we are about to establish a hemophilia registry and at the end the consensus was that the registry should be managed by an independent institute, and

this is of course the Paul Ehrlich Institute. So we are about to establish something like that in Germany. Another important point which is of course discussed very heartily also in Germany is the strict protection of personal informational patient rights. That is very important to get really compliance with the registry. We need clear rules for access to the data and, also very important, clear rules for the publication of any results of the data we get. So this is just to tell you that registries is very attractive and a very good way, but it is also not an easy way. We also have to work on that to be successful.

(Slide.)

So I come to the last slide and, you know, shortly before lunch, and the summary. In case of very rare protein deficiencies, as I showed also yesterday, you cannot reasonably expect to have comprehensive data before licensing. It is of particular importance to collect information about treatment in the post-licensure period, and this should be as complete as possible and should follow predefined procedures and rules and definitions. Pharmaco-clinical or pharmaco-epidemiological studies are difficult to apply, at least in very rare, hyper, super rare diseases, and patient registries appear to be really and attractive idea and maybe important and helpful, but particularly the

cooperation of patients and treating physicians is crucial. Thank you very much for your attention.

(Applause.)

DR. JAIN: Any questions before lunch?

(Laughter.)

DR. JAIN: I guess now we can break for lunch and we come back here in 45 minutes. That is 1:45 approximately.

(Whereupon, a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

DR. JAIN: Two minutes late I think. Good afternoon. I hope everyone had a very good lunch and is all awake and alert for the next session. This next session also is a continuation of the post-licensure data collection, and we have a change in our speakers because of, you know, being able to catch the plane on time. Dr. Robert A. Sandhaus will be speaker first, and his topic is an alpha-1 safety surveillance program.

An Alpha-1 Safety Surveillance Program

Robert A. Sandhaus, MD, PhD

DR. SANDHAUS: Thank you very much, and thank you to the previous speakers who were scheduled for this time for letting me jump in here. The advantage they will have is it will give people time to trickle in to their talk.

(Slide.)

I wanted to explain a little bit about the numerous affiliations listed there. I am Professor of Medicine and Director of the Alpha-1 Program at National Jewish Medical and Research Center in Denver where I have been running the Alpha-1 Program for the last 25 years, following the largest

continuously followed group of alpha-1 families in the country. The AlphaNet and the Alpha-1 Foundation are sister not-for-profit organizations. AlphaNet as I will mention to you during the presentation does prospective followup of approximately 2,600 alpha-1 patients on augmentation therapy, and the Alpha-1 Foundation uses the money that AlphaNet makes doing that and combines it with donations to support research through grants and scientific meetings in alpha-1 antitrypsin deficiency. The two organizations are in Miami, so I get to split my time between some very nice US cities. I feel a little bit like a fish out of water here. I have nothing to do with any kind of hyper-rare coagulopathy. I suppose that when you will hear the numbers that I am talking about I imagine you would classify us as being hypo-rare or perhaps infra-rare.

(Laughter.)

But just the same, I think you will find some interesting parallels, and just to top that off of course alpha-1 antitrypsin is one of the primordial serpents. Serum proteinase inhibitors and serum proteinase play a major role in coagulation.

(Slide.)

So what is this deficiency? A very rapid alpha-101. Genetic hereditary condition causing decreased

levels of alpha-1 antitrypsin in blood and tissues. The cause of the deficiency is a misfolding of the mutant alpha-1 protein during synthesis that allows it to aggregate in the endoplastic reticulum of hepatocytes and prevents its release in sufficient quantities to protect the other tissues of the body. This is probably also the cause of the liver disease associated with alpha-1. Current prevalence status suggests there are about 20 million individuals in the US who carry at least one mutant gene compared to the normal, and alpha-1 antitrypsin deficiency predisposes to destructive lung disease such as emphysema, liver disease in the form of neonatal, hepatitis, cirrhosis and adult cirrhosis, and other conditions including necrotizing panniculitis and Wegener's granulomatosis. There are over 100 different mutations of the alpha-1 gene that have been identified, and of those right now 34 of them have been associated with a quantitative deficiency in the blood of alpha-1 antitrypsin or normal levels of a dysfunctional protein.

(Slide.)

The phenotypes are identified by letters of the alphabet. In an assay which is actually an isolectric focusing gel that was designed to put the normal alpha-1 in the middle and thus was labeled M, and the most common, severely deficient phenotype in the United States is the Z

phenotype. My son is dressed in a Viking costume because all indications are that mutation of the alpha-1 gene originally occurred about 1,000 generations ago in the Scandinavian peninsula and has a distribution roughly to the equivalent of the Viking conquest across Northern Europe, the UK, Ireland, and on into the New World. Not that the Vikings conquered the New World, but that thing.

(Slide.)

Now we would all like to talk about our numbers. Blood bank studies in the US have suggested that there are about 100,000 individuals in the US with a severe deficiency of alpha-1, and there appears to be a similar number in Europe. We have the typical iceberg. You know, we are not an entity like protein C deficiency where you know every patient in the country that has it, although I might question that. But we have identified about 5- to 6,000 individuals in the country with severe deficiency, leaving about 95 percent of those predicted to have the disease or at least the condition unidentified.

(Slide.)

The issue for us of course is that this may actually be an underestimate, because recent evidence suggests that somewhere between one and two percent of individuals with the diagnosis of COPD in the US actually

have undetected alpha-1 antitrypsin deficiency; and if you take one percent of the 15 million people with COPD in the country, you get 150,000 individuals with lung disease and alpha-1. That doesn't even account for the people who are asymptomatic, have liver disease or some other presentation. So this in fact may be an underestimate. In fact, it may be a gross underestimate. One explanation for this discrepancy in the numbers is that since the 100,000 number is based on healthy blood bank donors it may be simply the bias of evaluating a healthy population of blood bank donors when most individuals might in fact be ill with their diseases caused by this condition.

(Slide.)

Alpha-1 antitrypsin, the protein, as you can see if you remember the diagram that was shown of antithrombin III is very similar. Primordial as I said, serpin with a bait loop here that likes to be chewed on by especially neutrophil elastase. It is a glycoprotein. It is coded for by a single gene on the long arm of chromosome 14.

(Slide.)

Augmentation therapy for alpha-1 has a very interesting history which I think is illustrative for many of the points that were raised during the course of this conference. In the 1980s the initial studies evaluating the

possibility of using augmentation therapy to supplement the alpha-1 in the blood of individuals with alpha-1 antitrypsin was embarked upon. The NIH evaluated purified alpha-1 derived from healthy volunteer donors who were mostly people working in the labs at the NIH, and a purification method was worked out as well as dosing trials to evaluate what sort of dose or regiment might be required to maintain a level that was predicted to be protective. That predicted protective level has been a source of constant confusion and questioning over the years since those studies were done. No one is really sure what the right dose of augmentation therapy is, but we are sort of stuck with the dosing that was first evaluated at the NIH in the 1980s.

We attempted to get plasma producers interested in moving this forward as a potential drug in the early 1980s. They were in the midst of trying to figure out why hemophilia patients were dying from plasma infusions and said basically, "We’re not interested in getting involve in another plasma protein product." But once the HIV story was a little better understood, we were able to interest Cutter Laboratories. As was mentioned earlier, Cutter went to the FDA, the FDA convened, and NIH helped convene an NIH conference to try to decide what the approval process for augmentation therapy in alpha-1 should be. It was decided that an efficacy trial

could not be completed because of the small number of patients that had been identified at that time with alpha-1 antitrypsin deficiency. There were only about 200 individuals as I mentioned in my comments yesterday, and so the drug was approved in a manner that even though the Modernization Act was long in the future that essentially looks a lot like the accelerated approval processes we have today.

The drug was approved based on the surrogate endpoint of biochemical efficacy that this drug tended to normalize the levels in lung and blood of individuals with alpha-1 antitrypsin deficiency and was safe, and there was a post-marketing commitment that was demanded as part of that approval process. That post-marketing commitment was that the manufacturer and the NIH would agree to cosponsor a registry looking at the natural history of alpha-1 antitrypsin deficiency over a minimum of five years and enrolling a minimum of 1,000 individuals with alpha-1, which implied obviously that a great deal of work had to be done to detect new patients. In fact, that registry was completed. It took place from about 1988 through 1995, enrolled 1,129 patients and followed them with pulmonary function testing and laboratory evaluation over the course of their time in the registry; and also took it upon itself, although it was

not designed to be an efficacy trial, to evaluate how patients did on and off augmentation therapy and showed in a case-controlled manner that augmentation therapy was effective at reducing the rate of decline of lung function in certain subgroups of the population and in reducing the mortality of individuals who were on augmentation therapy compared to those who weren't on augmentation therapy.

There are obvious biases in that study. It was not randomized, and so there are many reasons that someone would or would not be on augmentation therapy that might bias the results. But at the time, that combined with the German registry data that showed virtually exactly the same thing gave us confidence in the efficacy of this drug.

So in 1987, December of '87, marketing approval was granted to Cutter Labs to market Prolastin, our first and only product for many years. Cutter became Miles, Miles became Bayer, Bayer has recently become Talecris, so continuing the march through these companies. The 1990s were characterized by shortages as we identified more patients and often apparently due to inequities in the distribution system in the United States, and so in 1999 in response to the demands of the community a system of direct-to-consumer allocation of drug was developed which commercially was named Bayer Direct, but which was administered by AlphaNet. Thus

AlphaNet's ability to raise money to donate to the Alpha-1 Foundation. Then most recently and also with great excitement in 2003 two new products were approved for augmentation therapy, intravenously once a week at 60 milligrams per kilogram as Prolastin is dosed, came on the market. Aralast which was developed initially by Alpha Therapeutics and is now marketed by Baxter, and Zemaira, which went through the Sention*, Aventis Behring, ZLB Behring trio of company names.

(Slide.)

So what do we expect augmentation therapy to do? I have modified the classic Fletcher-Peto diagram which may not be so classic anymore to people dealing with hematology. But basically the Fletcher-Peto diagram is intended to show that as people age, beginning at about age 20, their lung function measured along the ordinate declines. That is the normal decline in lung function, and in fact emphysema is in many ways an acceleration of the normal aging process of the lung. The Fletcher-Peto diagram was intended to show what happens when someone smokes cigarettes, but I have modified that to instead of labeling this curve as someone who smokes cigarettes I have labeled it as someone who is alpha-1 antitrypsin deficient versus someone who has normal alpha-1 antitrypsin. Their rate of decline of lung function is

accelerated, and our expectation of augmentation therapy and the data done on now seven case-controlled trials with augmentation therapy has demonstrated that what augmentation therapy does is halts or slows the progression of that. It doesn't return lung to normal function since in general emphysema is an irreversible condition, but it does slow the rate of decline back towards normal. Obviously the earlier you make the diagnosis the more lung function can be preserved.

(Slide.)

We also have a brand new standards document, put out by the American Thoracic Society and European Respiratory Society and endorsed by the American Association of Respiratory Care and the American College of Chest Physicians, which defines in an evidence-based 83-page document the current standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. One of the most important aspects of this is that it says that all individuals with COPD should be tested for this condition and all individuals with asthma that does not completely reverse with maximal medical therapy should be tested for alpha-1 antitrypsin deficiency.

(Slide.)

So the challenges, the challenges I have been asked

to speak about, have to do with evaluating safety in rare diseases. All of that, in case you didn't notice, was introduction; but fortunately the number of slides remaining is not that great. Alpha-1 antitrypsin deficiency is this hypo-rare condition with three plasma-derived therapeutics as the only available specific therapy. All the initial product as I mentioned was approved based on what amounts to a surrogate endpoint. No randomized control study has confirmed the efficacy of this drug, and the two new drugs have all been approved based on small, non-inferiority studies, both looking at both safety and the same surrogate endpoints as the original product, blood levels and lung levels of alpha-1 antitrypsin. However, all the companies make conflicting claims about their products, either related to their safety or potential half-life or potential efficacy. So the patient community and the physician community treating alpha-1 patients is in a little bit of disarray about how to choose an appropriate product for their patients. So a suggestion was made that it might be possible for the alpha-1 community to embark on a prospective safety evaluation since voluntary post-marketing surveillance may lack the power necessary for identification of safety issues in rare conditions like alpha-1 antitrypsin deficiency.

(Slide.)

We thought we would take advantage of the AlphaNet patient population. AlphaNet follows approximately 2,600 individuals with alpha-1 antitrypsin deficiency on augmentation therapy. It follows those patients on a regular basis. A monthly telephone call is made. Every alpha-1 patient is assigned to an AlphaNet disease management coordinator, who incidently happens to be an especially trained alpha-1 patient, and we have used this methodology for doing long-term outcome studies in our alpha-1 patient population. Most of these individuals have ongoing St. George respiratory questionnaire, quality of life tools being administered on a regular basis, SF36s, and some in-house developed questionnaires. So the idea was to take this same group of patients, and they represent virtually all of the patients on two out of the three drugs currently available to treat alpha-1, and to develop in conjunction with all three manufacturers perhaps a single page or at least a short consensus questionnaire agreed to by all concerned, and administer that on a monthly basis by telephone, something we do on a regular basis with all of our patients anyway.

We suggested that this might facilitate reporting to sponsors of potential safety issues and an overall assessment of safety of these drugs, and obviously to help identify any serious adverse events that might or might not

be drug related for immediate reporting to the sponsors. We would give the sponsors summary data and presumably reserve the right to publish summary data about safety information.

Now we did suggest as part of our program that we did consult with the FDA to see if they might have an interest in helping us promote this safety surveillance program. But unfortunately since it is outside the regulatory recommendations for post-marketing surveillance, while they had a positive response to our intention to try to get this going, that was about as far as they could go.

(Slide.)

Our expect outcomes from such a safety surveillance study are the documentation of augmentation therapy and identification of class-specific, product-specific, lot-specific and/or patient-specific potential safety issues, and to do that in a timely fashion in a prospective manner.

(Slide.)

But there are issues obviously with any kind of safety studies along these lines, especially one that requires voluntary participation by sponsors. The protocol may not be acceptable to all sponsors, although all three drug companies have expressed an interest in evaluating the protocol to see if it will meet their needs for evaluation of safety. There is obviously a concern on the part of all

sponsors as to whether the potential cost of such a study could be justified by the benefits that could be moved forward with it, and prospective safety monitoring may disadvantage participants if not all products are involved in the prospective study because it would disadvantage those who participated in the studies if you compare their safety with someone who is still -- with a company that is still relying on voluntary safety reporting since the expectation would be that regardless of the safety overall of the class of product that there would be fewer reports of safety issues under the voluntary system.

(Slide.)

So in conclusion, safety of plasma products for rare conditions may be better evaluated using a prospective protocol, and this may be especially true for products with the types of excellent safety records that the alpha-1 plasma therapeutics have, especially since we have relatively large numbers of patients -- I am learning. I always thought I was a really rare disease -- and also since we have the built-in infrastructure to actually collect this data on a prospective basis. As you can tell, this is a protocol that is still winding its way through consideration by potential sponsors of the study, and I will certainly provide an update as this study moves forward. We will do the study because the

patient community needs it to be done. The only question is who will cooperate with the study and who will not. Thanks very much.

(Applause.)

DR. JAIN: I think in the interest of time maybe we will save our questions until the end.

MR. : He won't be available.

DR. JAIN: Oh, you will not be available? Oh, okay.

DR. SANDHAUS: You know, the good news is I hopefully kept my presentation short. The bad news is I am on my way to the airport.

DR. JAIN: Oh, okay. So maybe we can take one or two questions.

MR. : I am just very curious. Outstanding presentation, and as far as the cooperation with the community, what do you attribute that to as far as being able to do the monthly telephone interviews and then also the distribution? Because we do see this distribution problem in other plasma products, and it seems to be that alpha-1 individuals have overcome this problem.

DR. SANDHAUS: I think that one of the issues in alpha-1 that made the distribution system a success was the fact, number one, that there was a single product at the time

this was institute, and, number two, the distribution anomalies were so severe that the community was anxious to accept a direct distribution system. When we combined that with a system in which as a patient consented or authorized treatment authorization, the treatment authorization included authorization to be followed by AlphaNet. Now there was the opportunity to opt out of that authorization, but over the years there has been more than 2,700 patients. Some have died, some have, you know, left. But of the 2,700 patients who were presented with the opportunity to opt in to AlphaNet, 22 patients opted out. So I think some of it has to do with the sense of altruism among patients with a genetic condition because they appreciate, and we certainly emphasize, that the cooperation that they provide in these kind of studies not only has the potential to affect the, but also to affect their children and grandchildren. Yes, Donna?

DR. DiMICHELE: A couple of questions. How are you finding this? Why did you choose to poll patients for the data as opposed to doing data collection from medical records and doing this with their physicians? And do you anticipate since ultimately you want to publish this, in the absence of an IRB -- or I don't know. Unless this is an IRB-approved protocol -- it is?

DR. SANDHAUS: Yes.

DR. DiMICHELE: How are you going to get around the issues of publication which are going to be very important in this, and, you know, complicate the whole issue of doing registries and post-marketing surveillance?

DR. SANDHAUS: Actually our problem is that we multiple IRB aspects to this. The way that we first question, the way that we fund this is, number one, sponsors have paid for the disease management aspect of this. In the background of one of the slides you might have seen a big notebook. We have a 750-page document that we fondly call the BFRG, the Big Fat Reference Guide to alpha-1, which is aimed squarely at patients after a pilot study showed that physicians would love to have a disease management program to put on their shelves and never use, and which I encourage you to visit. You can actually see the BFRG on the web at www.alphanet.org. Just click on BFRG and sign your name and you can search, see a searchable version of BFRG.

So we get paid for disease management. We get paid to do -- we have grants to do studies, we get paid to do studies, and AlphaNet also acts as a CRO. Many of the trials that lead to the approval of the new products, and some products that are still winding their way through the process, have been done through AlphaNet acting as a CRO. I should mention that we also have an independent, but

foundation-sponsored, registry of about 3,000 patients with alpha-1. That is not the same group of patients, although there is some overlap, and that registry is filled with people -- in order to participate in the registry you have to sign a consent that you are willing to consider participation in clinical trials and accept mailings describing potential clinical trials that someone might participate in.

So for instance, when we did an IRB-sponsored 1,500 patient exacerbation study through AlphaNet it took us two months to enroll 1,500 patients. Our outcome study of over 1,000 patients which involves monthly questionnaires, St. George respiratory questionnaires, trough blood levels, all these kind of things, again IRB approved, we enrolled those 1,000 individuals in four months. It would have been shorter except HIPPA came into effect in the middle and we had to change our consent form. So was there something else you asked about?

DR. DiMICHELE: ---. (Away from mic.)

DR. SANDHAUS: Yes. Some of it is centralized western IRB as we have several, and some of it is through the University of Miami, which is where I co-investigate the outcome study with the faculty at the University of Miami, and so we put it through their IRB.

DR. DiMICHELE: Patient-based data collection

because you thought you would get more compliance than with physicians?

DR. SANDHAUS: Absolutely. That was just a -- it sort of came about because of Bayer Direct, and we have decided -- for instance, just as a quick response, for instance when we designed the outcome study we discarded the use of the chronic respiratory disease questionnaire because it had never been validated for telephonic administration, whereas the other two tools had been. Thank you.

DR. JAIN: Thank you, and have a safe journey. Our next speaker Dr. Abshire, and he is going tell us about the challenges of post-licensure data collection.

The Challenges of Post-Licensure Data Collection

Thomas Abshire, MD

DR. ABSHIRE: Thank you. It is always a mixed blessing talking after lunch. You have had a chance to stretch, but about right now the old --- effect is setting in, and hopefully you won’t fall asleep during this presentation. This presentation could also aptly be called the challenges of performing clinical trials within the hemophilic community in the United States, and I am going to give you our experience within the Hemophilia and Thrombosis Research Society in working with industry in achieving hopefully mutually beneficial goals.

(Slide.)

As you can see from the first slide, the mission of the Hemophilia and Thrombosis Research Society is two-fold. Really to promote cooperative clinical research in a peer-reviewed environment. We do have a modicum of funding that we do distribute under -- after protocols are asked for, looked at, and sort of an NIH peer-reviewed format. Also our second goal is to develop junior investigators. Both of these are very important to us in our fledgling organization. We have about 300 members in our organization, mostly physicians, but other health professionals, and they are comprised of both physicians from industry as well as academics and private practice.

(Slide.)

The registry was conceived approximately six years ago by Joan Gill and Craig Kessler, both founding members of HTRS, in thinking of ways to expand our clinical trials capability. Also Novo Nordisk was at the same time looking at how they might meet some of the requirements.

This little microphone is about ready to disappear underneath the desk here. It looks like it is going to fall down in a hole. Is it? I just pulled it out. Okay. All right. I am sorry. It was like a little chipmonk was pulling it down or something underneath here.

(Laughter.)

I don’t know what it was. You know, like that little woodchuck or something. Okay.

(Slide.)

So their goal was to be able to meet FDA post-marketing commitment. Now you perhaps would ask what is the motivation from each, the standpoint of each organization. Well, our motivation was without money there is no mention. Actually for those of you who do not know who said that, it was Mother Teresa. Mother Teresa was speaking of her mission, her mission in India. But really any kind of mission, whatever you are embarking on, is irrelevant if you don’t have the resources to accomplish it. As probably you gathered from the presentations just before lunch, I nicely put here I think Novo Nordisk motivation was honoring a commitment to the FDA; but I look at it as pure fear factor, so that is my interpretation. After realizing they could yank your license or do all sorts of other stuff I would probably want to honor that commitment, too.

(Slide.)

So the mission of the registry was, however, to a collaborative effort both between our organization and Novo Nordisk to work with hemophilia treatment centers to look at the pathophysiology of disease and also the safety and

efficacy of different treatment regiments. The emphasis, and this is a no-brainer as you might imagine working with Novo Nordisk, was to focus -- not exclusively, but to focus on factor VIII and IX inhibitor patients.

(Slide.)

So several partnerships were required to achieve this goal. The first is our part within HTRS. We had contracts that we initiated through each of the treatment centers and other institutions that maybe were not a treatment center, and then each of the institutions were required to send data in on their patients. We as an organization owned this data and oversaw the research that was going on and always were conducting the research.

Covance is an organization that helps manage data, and they helped develop the software for the program. Helped collect, manage, and transmit the data, and this was certainly HIPPA compliant, and also maintained that serve in the sky so to speak that the data went to which was completely secure and, as I mentioned, HIPPA compliant.

Novo Nordisk, as my previous slide alluded to, provided the funds, the resources in an restricted fashion. And they also were able to get information that they would then use to the FDA on factor VIIa, recombinant factor VIIa aggregate data regarding safety outcomes and efficacy.

(Slide.)

So eligibility was basically anybody with a bleeding disorder, whether it was congenital or acquired. This included both factor deficiency patients with inhibitors and any bleeding disorder that used VIIa for example for platelet dysfunction.

(Slide.)

The reason why we did this was because we wanted people to register patients, as many patients as possible. We will show at the end why there are some of the difficulties with this, but there was certainly reimbursement for patient registration which is a key element. This included any kind of registration for any bleeding disorder patient. Then there was reimbursement for specific individual bleeding episodes which focused on inhibitor patients and also on the use of recombinant VIIa. So there was an extra motivation for putting in data for patients with inhibitors and were using the product for reasons that should be obvious for all.

(Slide.)

This is these next three slides are just examples of this web-based program, how you registered patients. It was actually very user friendly, even for a stupid data entry person like me.

(Slide.)

It was pretty easy to do, and you could have on one of your -- there we go. You had your center's information and then so you could kind of see what was happening globally within the organization in terms of entry of data. Then we got to individual patients they remind you of patients that are still not complete in terms of their data entry form and those that were complete in terms of your institution.

(Slide.)

Now we looked at this data just now almost a little less than a month ago, but there were 609 patients that were registered from 57 sites. The number of sites that have been enrolling have been increasing by the month, but as I mentioned just a minute ago, this was closed as of mid May. There were 196 patients that experienced almost 2,000 bleeding episodes, so you can see here the discrepancy between registered patients and then specific patients who had bleeding data entered. Then there were about two-thirds of those patients, as you can see here -- you can't see the green very well -- that actually had acute bleed treated with recombinant factor VIIa. Analysis of this data has certainly been ongoing and submitted to the FDA, and there were three probably possible SAEs related to recombinant factor VIIa reported to data, and these were just mostly lack of effect

and no evidence of thrombosis for those of you in the community that have been concerned about that.

(Slide.)

What were some of the advantages of this registry? Well, first of all, it allowed us to have a longitudinal surveillance of both the safety and efficacy of different therapies, particularly recombinant VIIa, and it gave people an access within our organization on a national level to look at different treatment aspects and ask some clinical questions. We were able to generate one publication.

(Slide.)

This was an individual from Dr. Shapiro's center, and I have just summarized. This data was just published in March in Hemophilia. I have summarized it here for you, and you can actually see it a little bit better here than in the notes that you have, which is like you have to be able to use a magnifying glass to see that. So this data was collected over about a two-and-a-half year period. There is a typo on there. It is 2002. There were we based -- divided the patients between dosage range, between what is the FDA-approved range of 90 mcs per kilo, between 100 and 150, 150 and 200, and greater than 200 micrograms per kilogram per dose. There were 555 bleeding episodes in 38 patients that were studied for this first pass. You can see most of them

were spontaneous, but some were trauma related, and about a fifth were related to surgery or procedures. Most of these were at home, so these were self-reporting from the patients, and you can see that the efficacy was high as has been reported in previous reports for this product, 84 percent for the lower doses. But what was surprising for us, and this actually came out of some information out of Israel using what is called megadose, much higher doses of recombinant VIIa given once, that the efficacy of stopping bleeding was much, much higher. That was significant at P of less than 0.001. There were five patients who experience nine adverse events and most of these were related to -- almost all related to decreased response, just lack of efficacy.

So our conclusions from this initial look at the data was that this product can be used very effectively for hemophilia patients with inhibitors at home, that you can give sometimes rather high doses and have no side effect. Now granted these are a small number of patients, a small number of episodes. You can't really make broad generalizations about it. But what was surprising out of this was the dose range that was a higher dose certainly in people who are not at increased risk for thrombosis, i.e., not the elderly, that this might be the way to go. Although further study has to be accomplished to say that

conclusively, and that it looks like over this wide dosage range recombinant factor VIIa was quite safe.

(Slide.)

So what are some of the challenges that we have found in the registry? Well, first of all there -- and I think most importantly, they are resource constraints within most hemophilia treatment centers. For those of you who are not familiar with our community, the funding at the federal level has been flat-lined -- it is not like an EKG flat line, although so many people may think of it that way -- for the last 12 years from the CDC and from MCHB. So most centers have taken money through other resources, through PHS program and whatever other ways they can beg, borrow, or steal to support their center. So when you have a center that is a small center that is trying to take care of patients it is very difficult to enter any extra data.

Which leads me to my second point, that most people view this as another database, because those of us who get federal funding are committed to supporting the uniform data collection database, UDC. You will hear about that in just a minute for obvious reasons, and also every center usually has an institutional or regional database that they need to keep up. Participation is not universal because funding is -- quite frankly, even though funding is there it is not maybe

high enough to generate the kind of interest that you would like to see, and just through also lack of people to enter data. There is a perception in our community -- it is an interesting community, of how we exist with industry and also patients -- that there might be a perception of company involvement, although this, as I outlined earlier, is clearly not the case in terms of how we have set this up. Also some people are concerned that even though the data that Novo Nordisk looks at is de-identified, they can actually see what center it comes from, and some people are concerned about that. Although as I mentioned earlier, this is totally HIPPA compliant and not specific patient data. But for obvious reasons they need to know what is happening in the reports to the FDA.

(Slide.)

So in my last slide, what would I like to propose for the ideal system. Well, some of you in this room may know that we are working very -- in actually quite a developed way to develop a national database. This hopefully would be suitable for multiple tasks, including collecting information through the UDC, allowing people to manager their own patients at each center, and also helping us within HTRS and other organizations to perform clinical trials and allow industry to collect the data that is important for the FDA.

It would be important that this database would exist at a neutral site. Database/server that would not be conceived as being conflict of interest, and also to have what we would call non-aligned statistical support so that you don't necessarily have industry supporting statistical support, but completely at least from a perception standpoint non-aligned.

We would also, important, have an oversight committee that is over this that would comprise all the parties, including consumers. As you heard from the last presentation, the one model with alpha-1 antitrypsin has worked very well. Third, you need to have sufficient funding to allow this to occur and allow each of the centers to have a data entry person. As we talked about earlier, there needs to be streamlined IRB submission and approval, and this is a real opportunity just like the pediatric oncology group now known as the children's oncology group. An amalgamation of all the two the former groups are working on national IRBs so that you can have a template that can be used at different individual institutions.

Then finally, you know, we would really like to come up with a cool name fir this database. So if any of you have a cool idea for this you can send your ideas to me. That is just a joke, but -- okay. So that is all I have to say. Did you want to entertain any questions now or wait

until later?

DR. JAIN: --- question.

DR. ABSHIRE: Yes.

MR. GILLIAM: David Gilliam. I am interested a little in the financial incentive to patients. What is right, what is wrong in that? How much is okay, how much not okay? Can you elaborate on that.

DR. ABSHIRE: Yes. I was talking actually more about the financial incentive for the institutions managing the data, and not necessarily -- just enough to manage all of the IRB costs and the data entry personnel. I think in regard to patient-related things, I think IRBs are pretty clear about this, that it needs to be just enough to allow them to have their time and effort to come travel, to have blood drawn, et cetera, to be managed. But it cannot be perceived to be an inducement. That is actually pretty clear. See, it is a very, very narrow, ginger balance that you have to achieve there.

MR. GILLIAM: That is correct. Thanks.

DR. BRAUN: My question has to do with if you have a disease-specific registry that is related to the indication for the product, but you also have a lot of off-label use in other populations that don’t have that condition, how do you deal with that? That is a big concern.

DR. ABSHIRE: Yes, it is a very good question. It is a big concern for us from a clinical trial standpoint. I mean, right now because there is not a national database it is very difficult we think as clinician investigators to come up with that group data. We think that having a national database that we enter all kinds of patients, and granted you would have to decide if you want to include the Glanzmann's thrombasthenia for example as part of your bleeding disorders group of patients. But you are more likely in our estimation to get more accurate data if you broaden the picture and made it easier to extract data as opposed to what is happening now, which is really of your own good will entering data which is very selective.

MR. : Can I just followup on that quickly? So how generalizable do you think the findings are that you presented from your hemophilia patients to other conditions that might be treated with the product?

DR. ABSHIRE: You mean just totally non-bleeding disorder related patients? I think this idea of having interaction between patient groups, industry, and academia in coming up with a way to manage data, to provide information to patients, do clinical trials as you heard in the alpha-1 antitrypsin, I think is a very worthy idea to pursue. That is what we are trying to achieve within the hemophilia

community if we can pull it off. Partly it will be related to funding I think, like it is a lot of times.

DR. JAIN: Last question.

DR. ROSSI: Françoise Rossi. How did you decide for, what was the criteria you have, or did you have the definition for improved efficacy or higher efficacy at the time for bleeding, especially coming from the home treatment?

DR. ABSHIRE: Yes. It was related to patient questionnaires, to -- and a lot of hemophilia trials do this already where you will see there it is patient-related assessment of good, excellent, good, fair, poor, to response to one dose. So that is one, their assessment of it, and also how many doses were given to achieve a response. Okay. Thank you.

DR. JAIN: Thank you.

(Applause.)

DR. JAIN: Our next speaker today is Dr. Soucie, and he is going to -- I hope I got that right. He is going to talk about potential of CDC's UDC to capture post-marketing data.

Potential of CDC's UDC to Capture Post-Marketing Data

Michael Soucie, PhD

DR. SOUCIE: Good afternoon. I wanted to thank Dr. Weinstein and other organizers of this, too, for inviting

me to come and talk about a public health surveillance system that we put in place for the bleeding disorders community and to propose to you or discuss with you the possibility of using this system to perhaps do some of the things that we have been talking about during this conference in terms of doing a post-marketing data surveillance on people with rare bleeding disorders.

(Slide.)

By way of brief introduction, I am in the Division of Hereditary Blood Disorders at the Centers for Disease Control. It is a group of about 40 of us, epidemiologists, people in public health translation. We have epidemiology surveillance. We have two laboratories, a hemostasis lab that provides testing in support of projects, clinical projects. One of them is a hemostasis lab and the other is a molecular lab. I will briefly mention those a little bit later, and our mission as mandated by Congress as you see here is to reduce or prevent complications of hemophilia and other bleeding and clotting disorders and thalassemia.

(Slide.)

We try to accomplish this mission through the establishment of a public health surveillance system prevention program that revolves around a surveillance system for product safety among persons with bleeding disorders.

Eligibility for to be part of this surveillance system are that patients who receive care at a federally-supported comprehensive care treatment or hemophilia treatment center; patients have a congenital deficiency of any of the clotting factor proteins below 50 percent of normal; or a clinical diagnosis of Von Willebrand disease. This are our current criteria for eligibility, but they certainly are not set in stone and they can be modified based upon need.

(Slide.)

Our target priorities for this prevention program are the priorities set by the bleeding disorders community, and these are blood product safety, the issue of chronic joint disease, women with bleeding disorders and special issues that pertain to women, and the detection of hereditary abnormalities associated with bleeding and clotting disorders.

(Slide.)

We do this through a cooperative agreement mechanism in which we provide funding, as Dr. Abshire mentioned unfortunately flat for many years, but we don’t control Congress. Nobody does. However, we for that funding we asked that the treatment center staff participate with us in blood safety monitoring and surveillance efforts in the community to collaborate with lay organizations such as the

National Hemophilia Foundation to deliver consistent preventative prevention messages. These prevention methods, by the way, are based upon information that we get through our surveillance system, and so we then continue with the surveillance once the prevention messages are implemented to monitor the population to assess the efficacy of those prevention services. So the surveillance and the epidemiology and the public health translation all come together through this network and through this cooperative agreement.

(Slide.)

The blood drops in this map show the approximately 135 federally supported hemophilia treatment centers which are distributed very much like the population in the United States.

(Slide.)

The Universal Data Collection System, or UDC, its primary purpose, the reason it was set up, was to monitor blood safety among recipients of blood products, to monitor the extent and progression of joint disease, and to really importantly identify issues for further study.

(Slide.)

It is a national protocol. It is approved by CDC, and also the local human investigational review boards at

each of the 135 centers; and as everyone has alluded to, this is somewhat of a problem sometimes dealing with each of these, and it really almost is a full-time job keeping track of each of the 135 institutional review boards of the institutions that take part in the study. There is standardized data collection annually using tools designed with a large degree of input from experts in the field through a working group. A portion of the blood specimen that is taken at each annual visit is stored for future blood safety investigations, and the blood specimen is tested centrally for known infectious disease agents and new infections as a result of this testing is investigated very thoroughly for any possible link with product.

(Slide.)

Just briefly, the data elements that we collect include demographic information, clinical information in terms of the type of disorder severity of course, treatment information in terms of an estimate of how many bleeds and infusion frequency. All of the blood of the treatment products used during the year previous to the visit, and some particular information about infectious disease including liver disease and joint infections. We ask several questions about impact of joint disease on activities of daily living including days of work missed or school, and joint range-of-

motion measurements are taken by trained people according to established protocol.

(Slide.)

I will give you a little idea of participation in this project since May of 1998. Over 16,000 persons with bleeding disorders have been enrolled, and I will give you a little idea of the distribution of the disorders in just a moment. Right now I just want to make an impact on you how much the community, both the bleeding disorders community and the treatment center providers, have gotten behind this project. There have been more that 40,000 UDC visits by these 16,000 individuals, and the overall national refusal rate because it does require informed consent is at a remarkably low 7.6 percent, which we take as being a real sort of a -- I have lost the word, but really a buy-in by the population that this is something that is really important and something to participate in. At this time we are as has been mentioned switching over to an electronic data system. Up to this point it has been paper and pencil forms.

(Slide.)

So we had to start out somewhere with an electronically -- with a clinical software tool, which is we believe going to make a large impact in what we are going to be able to do with this surveillance system in terms of

facilitating data sharing among the various treatment centers, being able to perhaps make some efficiencies in our data collection efforts. We won't have to have all centers collecting all the same in formation. We will be able to have more data collected more efficiently and not increase the burden of data collection on the treatment centers. We believe it will help facilitate identification of new areas and patient populations for further study, and we will come back to that in just a second, and more opportunities to extend the surveillance into new areas. In particular, I would like to describe for you an inhibitor project.

(Slide.)

As Dr. Seitz sort of mentioned earlier and eloquently stated all of the problems with studying inhibitors in previously treated patients, we are doing a pilot study with 10 of the hemophilia treatment centers to enroll 50 patients over the next year. The purpose of this project is to really work out the details of how we can use this surveillance system to try to address a really difficult situation of a rare outcome in a rare disease, if you will, these inhibitors in previously-treatment patients to really try to get the detailed data that is necessary to be able to study them. Not only that, we have committed to doing centralized inhibitor testing at the CDC in our hemostasis

lab to get to the issues of differences in inhibitor titers depending upon where they are measured. We are also committed from our molecule lab to do hemophilia gene sequencing to get at the issue of the genetic possible relationship with inhibitors, and we are doing this with funding, grateful funding, from Wyeth Pharmaceuticals to help us to provide data coordinators to help the treatment centers to collect the most difficult part of the study, which is the exposure data.

(Slide.)

What that consists of is getting the information about every infusion that patients take. Not only the brand, but the amount, lot number, and reason that the got the infusion. These are all issues that have been raised as potential risk factors for inhibitors. The other thing that is going on are methodologies to try and work this out to where we can get these data in the treatment centers setting, how we can get the specimens most easily transported to CDC with the results being quantitatively correct, but also being doable and economical, and when fully implemented this will provide post-market surveillance for inhibitors. As we progress here through the years we are hoping that more funding will become available, we will be bringing more treatment centers onto the project and be able to try to

answer some of these difficult questions about inhibitors.

(Slide.)

I say all this to really sort of bring it back to the focus of this conference, which is rare bleeding disorders, and I mentioned to you that I tell you the patient distribution. You can see largely is a hemophilia population because quite frankly it was set up to address most of the issues that were of most concern to the hemophilia patients, but I would point out the three percent there.

(Slide.)

Those three-percent of patients are some of the patients that we have been talking about at this conference. I would just point out in the first column here we have the results of a report that we get every year from the hemophilia treatment centers that gives us the number of patients that they are actually following for their disorders. I would just point out Dr. Rossi gave some data earlier, an estimate of how many patients, and this is in actual fact the number of patients that the treatment centers are reporting. In all cases they are higher numbers, and in some cases quite a bit higher numbers than your estimates.

In the second column we have the number of patients that have been enrolled in the UDC, and this is without really any attempt to ask the treatment centers to enroll

these patients preferentially. So certainly this proportion, which varies between as you can see 16 percent for factor II patients up to 40 percent for factor X patients, this could conceivably be brought up close to 100 percent for all of these factor deficiencies.

(Slide.)

In addition to the information I showed you earlier that we collect about all patients, I just thought it might be informative to give you a couple of examples of some of the data. We do collect information about the number of bleeds that people report over a six-month period and we also collect our information about the factor products used by the patients, and so I thought it might be useful just to give you a couple of examples. Here is factor X. As we have all heard at the conference, there is really no product for this, no specific product at least in the United States. The patients in this report, on average 4.9 bleeds over a six-month period with a range as you can see of no bleeding up to just about every-other day. Among that group you can see that there are 14 patients had received at some point during the previous year prothrombiin complex concentrates. A number received fresh-frozen plasma, a couple DDAVP, and some patients Amicar.

(Slide.)

On the other hand we have our factor XIII patients, and you can see the 40 patients who have enrolled in UDC have much less tendency to bleed. Reported bleeds, the average is two with a much smaller range, but the range of materials being provided to these patients is a little bit more broad and there is a factor XIII product available that 25 of these patients have received. So I just wanted to just show that information. Of course, all the other data we have for all the patients we have for these patients as well, including joint range-of-motion measurements and so on.

(Slide.)

We have used the information from the universal data collection project to not only embark on the post-marketing surveillance for inhibitors, and I might add that this has been done in conjunction with and along with recommendations from the FDA in terms of what they would like to see in terms of post-marketing surveillance for inhibitors, and also with an eye towards the international community. Dr. Donna DiMichele has been helping us to identify registries and other projects throughout the world to make sure that we are collecting data similar to that in other countries so that the data eventually could be pooled.

Other situations, we have tried to use the data to help investigators to identify subpopulations that require

further study. As you recall, this is one of the goals that we had for this project. It allows us to be able to identify treatment centers who may have populations of interest for particular studies. For example, women with hemophilia or patients with hepatitis C who meet certain criteria.

(Slide.)

Really our vision for this project as Dr. Abshire has really already alluded to is to have an enhanced collaboration among the providers, among industry and government, to come really to grips with a national research agenda and to really hopefully recognize the universal data collection project as a national data repository, one which can be used for a lot of different projects. However, as Dr. Abshire also mentioned, it needs to have a nationally recognized oversight body with representation from all the stakeholders. I mean all the stakeholders have to be at the table, and I will tell you a little bit in just a minute about efforts along those lines.

The uniformed national database we believe is really already in place, and a web interface to this national database is in the planning stages and we are working on that issue. We would hope that we utilize the universal data collection project as a resource to stimulate research questions and to identify study cohorts.

(Slide.)

How do we get there? We have already had a couple of what we refer to as data summits where we had people from the hemophilia treatment center community, and these groups from this community have arrived at a consensus that this is really a good idea. Our accomplishments to date have been the identification of the major tasks that need to be performed to make this a reality, and we have some seed money. As everyone keeps saying, money, money, money. It takes money to do these things. We have seed money from HOG. That is the Hemophilia of Georgia, not the bovine variety. It is not even bovine. It is porcine, isn't it?

(Laughter.)

I am mixing my terms, but this is the Hemophilia of Georgia has generously donated seed money to provide an infrastructure for this data oversight body, and subcommittee formation is to start very soon.

(Slide.)

In conclusion, we believe that the UDC is a valuable public health tool that provides our program -- it actually helps our program to address our mandate from Congress to identify risk factors for complications, to monitor the effectiveness of interventions that we apply through the community, the hemophilia treatment center

community, and this system is being expanded to serve the need of the whole bleeding disorders community. Thank you.

(Applause.)

DR. JAIN: Time for one question.

MS. : I have a cultural question. I wonder how it is perceived that such an institution as CDC can be -- have one of the studies or program funded by only one pharmaceutical company. Is it something usual? Is it --?

DR. SOUCIE: That particular study, this whole surveillance system, is not supported by Wyeth. The universal data collection system since 1998 has been entirely supported by CDC. This inhibitor pilot project has been funded by Wyeth and this is an opportunity to provide funding, necessary funding to be able to do the data collection in the treatment center environment. So it is a industry-government collaboration. It is really a demonstration project to show how this might work in other situations such as rare bleeding disorders.

MS. : Yes, and I understand the concept and practical aspect of it. I am just wondering that such issues have been brought up in other situations. In France, for example, where there is a concern to have only one company sponsoring a project.

DR. ABSHIRE: A followup question on that, because

we were concerned in developing this database of similar perception, and negotiations are in way to approach the other four large pharmaceutical companies, Novo Nordisk, Baxter, --- and Behring also to solicit their input, and we are close to finalizing those negotiations. So that all of the five major manufacturers at least in the United States would be at the table and have a vested interest in this national database in funding it.

DR. SOUCIE: Yes, and one other point about that is that we have gone to all the manufacturers and presented the same opportunities, and again this is the -- the first year is just the pilot, but obviously to be able to bring this project to all 135 centers is going to require much more funding than just one company is going to be willing to provide. So the plan is as Dr. Abshire points out is hopefully this will be expanded.

MS. : I was wondering how was the level of the severity of the patient included in your registry. Are they severe, or are they including mild and moderate patients?

DR. SOUCIE: You are wondering how much data we have about the severity?

MS. : How much percent of these patients has severe deficiency of a single deficiency?

DR. SOUCIE: What we are collecting currently in terms of markers of severity is baseline factor activity level, and that is been applied, you know, mostly for the factor XIII and factor IX. In terms of the other factor deficiencies, presumably those measurements are being filled in there. But again, we haven't done as much with that data as we have with hemophilia data. So I can't tell you exactly offhand, but --.

DR. DiMICHELE: Can I just clarify? I think what you are asking is are we collecting heterozygous as well as homozygous data for rare -- and I think people are submitting everything at this point, and I don't think you have done the subanalysis of that, how many are severe in terms of less than one percent or with a rare bleeding disorder compared to other levels. Is that correct?

DR. SOUCIE: Yes. The eligibility criteria I gave you and pretty much the centers are deciding which patients they choose to enroll, and so that is something that we will have to look at as we get more into this area.

DR. JAIN: Thank you. Our next speaker is Dr. Peyvandi. She is going to tell us about the Italian experience of an international registry for these rare bleeding disorders.

(Adjusting equipment.)

International Registry of Rare Bleeding Disorders

Italian Experience

Flora Peyvandi, MD

DR. PEYVANDI: Good afternoon, everybody, and thank you very much still to be present. I am sure you are tired, and I hope to be very short. What I am going to present in these 15 minutes is what was our experience in the last 10 years based on the rare bleeding disorder and collecting the information from different parts of the world.

(Slide.)

All these data was done because we think at this point of time as was mentioned yesterday the few centers and few data collection centers is not enough to give us enough information. And all of us we have heard in these two days it is important to have a unique global or international registry or database containing all the information regards the clinical manifestation, the best types of diagnoses, the standardization of the phenotype and genotype result of the patient, which is the best type of treatment, and also to analyze how much --- we need and what type of --- we have to do, and how many patients we have located in different parts of the world.

(Slide.)

So to be able to answer to all these questions we

had to look to all the existing registries, and first of all I started with ISTH registries and how we can see there are different types of registries under the SSC database containing factor IX database, other clotting factor concentrate, factor S deficiency, Von Willebrand database, and also other types of registry based on the single time of disorders.

(Slide.)

A part of ISTH database, they were also existing other databases in the literature, mostly based on the genetic abnormality of each single disorder.

(Slide.)

And here you can see the factor XIII deficiency by ETRO group working party, the international factor VII deficiency organized by Dr. Mariani*, other factor VII deficiency --- registry, the national registry of factor VII in Slovakia and other factor X deficiency. As you can see, there are few factor deficiency registries available in the world, but unfortunately when you are going to get the information and to make the query as a clinician how to treat this paper, which is the best way to make the diagnosis, so which is the difference of using the different thromboplastin to make the best type of diagnosis. There are few type of available data and query that you can make as a clinician.

(Slide.)

We have fortunately a good database organized for the United States and for Canada which contain a base organization of the rare bleeding disorder with all clinical manifestation and the phenotype analysis. But still this database is missing the genetic alteration in these patients.

(Slide.)

So the state of the art is existing databases and registries are prevalently based on the data collection about unique coagulation factor or disorder. The genotype data associated to phenotypic features are generally collected, but no clinical treatment data are reported in the same registry. There is no possibility as I was mentioning before to do any type of query or to ask any report from these databases.

(Slide.)

So the databases available online are usually consulted in order to gain information on genes or the proteins.

(Slide.)

So why is it important to have an international registry and what we can use as Italian experience.

(Slide.)

We try to answer why do we need to establish this

international registry.

(Slide.)

Because we think from 1995 there was a really considerable increase in clinical information in the last three years because people started to make the molecular analysis.

(Slide.)

We all now have considerable information located in different registries. For example in our group, we made the database, the national database, as the first step in hemophilia center of Milan where I am working trying to get information from different parts of the world as you can see. But still somehow two years ago I had the feeling that this information is not open to all other researchers in the world and they cannot use the information which is located in this center.

(Slide.)

So we used a lot of information getting from the Middle East area and South India for the higher incidence in this area which helped us to increase our knowledge in this field. Our center, as different groups in the world, started collecting information and making and developing international collaborations with the rare bleeding disorders and making a network and becoming an international reference

point.

(Slide.)

Now I think the various groups spread al over the world, they deal with rare bleeding disorders from different points of view as was seen before, the clinical, phenotypical and genetical point of view.

(Slide.)

It would be really useful to create a network link as to provide the relevant exchange and extension of findings.

(Slide.)

So this new model that we developed could be only the starting point and of course is going to be open for all type of comments and every type of help could come from each single center, hemophilia center or even every organizer in the world could help us to improve this database. This was born with an aim to efficiently organize and extract the consistent amount of information on the diagnosis, treatment, and prevention of rare bleeding disorders using the genetic abnormality and mostly frequent in some area of the world.

(Slide.)

The flow chart based in this database is based on the clinical information and pedigree of the patient, the phenotype analysis, including the functional assay, and ELISA

assay just to be able to distinguish the type I deficiency from type II deficiency. The genotype analysis and also of course in the future will be done the haplotype analysis, which could be the best model for the prevention in the countries with the low resources, economical resources for this type of abnormality. The most important point, every single clinician could be able to ask the query of report from these data.

(Slide.)

Here you can find all the single information in the international database. The clinical information, the type of the bleeding, other type of disease like the liver disease or HIV or whatever the patient is affected, the genotype analysis, the type of the treatment, complication, and prenatal diagnosis it has been done or not, the family story, and the safety of the product which has been used.

(Slide.)

So this website, in two weeks time it will be available and could be organized as a first step we thought. We have to use only the one page, which is not going to get all the information that you have seen in the previous slide. The first work which has been done I think with the work with the ISTH working party is to understanding how many patients are located in the world and in which area of the world we

have more focus the number of the information, the patient affected by each single disorder.

(Slide.)

That is why we thought it could be useful to send a letter to all treatment centers registered to the World Federation of Hemophilia, introducing this new website and asking them if they are interested to join us just to explain how many patients they are seeing with each single disorder and how they are treated. If they have any available type of treatment like plasma, --- participate, each single type of concentrate. If this data has been already inserted in some other registry, national or international registry, and this could be the first step giving us the information to really know how much work needs to be done.

(Slide.)

These are the number of the centers around the world except the Unite States and Canada because I think there is a good organization here, and we could somehow link the information between these two or three organizations and trying to get the most important information. I think this information at the end could be important because this is what was seen before.

(Slide.)

Here it is. Okay.

(Slide.)

Then we come back again to this area. Okay. I think creating a cooperative network of hemophilia centers around the world will help us to fill the gap between data production and their accessibility.

(Slide.)

As you can see here, this is the top of the record that we are already able to extract and to understand what is the genetic abnormality of each single disorder because we were much more focused on the severe type of disorder.

(Slide.)

This would be available for each single clinician, and I think this is the most important tool for every different kind of information that was discussed in these two days. It would be important for clinicians. It would be important for the advocacy and for the pharmaceutical company for understanding really how much --- and how much --- has to make how is going to be the marketing issue for these type of disorders.

(Slide.)

At the end I think our work could represent the starting point for the establishment of an international database under the supervision of an international society such as World Federation of Hemophilia or International

Society of Thrombosis and Hemostasis. In order to create an international collaboration it will be necessary to build up a steering committee to my opinion composed by the experts around the world who work already and have experience in the clinical, treatment, and genotype and phenotype characterization.

(Slide.)

Of course, this goal as I mentioned before is important for the management of the patient and for implementation and getting the most useful information from all preexisting data. With this one I think I will just close my presentation, and thank you for your attention.

(Applause.)

DR. JAIN: Can I ask you a question? Who is going to fund this?

DR. ROSSI: Okay. When we started to make this international registry I had a young investigator grant from the buyer. The one is available from I think is three years, and that was the starting point. Of course for making such a registry it needs really big fund, and to my opinion as it was mentioned before, I am not sure if we can only base on the pharmaceutical company, and we need to have a neutral position. And trying to have help from the FDA, from the European grants, and from some other fund, and I have no

idea, but --.

DR. JAIN: I have another question. I think in one of your slides you mentioned you were --- to a North American database on rare bleeding disorder. Which database were you referencing?

DR. ROSSI: I think Donna can explain something in this North American/Canada database.

DR. DiMICHELE: This is a database -- I mean, it was published in 2004 and it was a North American collection of data on all rare bleeding disorders except for factor XI, which when you live in New York doesn't seem so rare I think sometimes. So I think we basically didn't include factor XI, but all other disorders were included, and this was a project that went on through the hemophilia and thrombosis research societies. So it actually represented a North American effort in order to characterize the patients in North America, and I just wanted to say, I mean, because I wanted to clarify. This was a database of, yes, you know, characterizing the epidemiology, characterizing the clinical manifestations, and although you said it didn't contain the genotype data, the genotype data was actually asked for, and at that time there was very little genotype data on the rare bleeding disorders. As a matter of fact, the database, if we looked at the reasons we established the database, they were

to not only characterize the patients in a way they had never been characterized before clinically with respect to bleeding manifestations, treatment practices and complications, but also to provide a database for clinical trials and to provide a database for genotype/phenotype correlation studies and to get laboratories interested in genotype studies.

So that actually has gone on since then, and the database has been used more than once to sort of understand how many patients with a particular disorder have been in there. So it was, you know, I think a good prototype study for North America and the kind of registry that we are now proposing doing internationally through the working party to even expand that database for many of the same purposes I think.

DR. JAIN: Thank you. Last speaker for the day before the panel discussion is Dr. Tellier from France, and she is going to tell us about analysis of a 10-year experience in France.

Analysis of a 10-Year Experience in France

Zéra Tellier, MD

DR. TELLIER: Good afternoon. I would like to thank the organizers for inviting me to present to you our experience in the collection and analysis of post-licensure data. A few words about the French historical background.

(Slide.)

As it was mentioned yesterday, the products I will talk about are available in France since the late ‘80s or the early ‘90s, and before 1994 they had the status of blood products. In 1994, the status changed. They become medicinal products. So we have long-term therapeutic experience in France with these products.

(Slide.)

I will give you some information regarding this experience. The first question that can be raised is what types of post-licensure data can we collect, and I tried to summarize here their input or advantage, their main limit or constraints, and our experience in these different types. Post-marketing surveys are a prospective collection of predefined data and local monitoring is often organized. Their main limit is that the exhaustiveness of the population is not guaranteed and they need a long-term cooperation with physicians. As it was mentioned this morning, there is an ongoing PMS with our factor VIII, factor IX, and Von Willebrand factor concentrates. Close to PMS, the followup of temporary utilization authorization and it is also a prospective collection, but with a simple CRF and frequent side effects may be detected with these types of personalized central data. I will present to you later our

experience with factor XI deficiency patients with our factor XI concentrate.

Retrospective studies, their main advantage is that data are available and they may allow long-term followup, but their main limit is that part of the data may be unavailable and it is very important to look for the exhaustiveness of the population very systematically in order to avoid any bias of selection of the patients. I will present you our experience in congenital protein C deficiency with our PC concentrate.

Pharmaco-vigilance allows the detection of expected and non-expected side effects, and its main limit is under notification and of course all products are submitted to pharmaco-vigilance. I mention here the LFB products that are used in rare bleeding or thrombotic disorders. Even if LFB is not involved in the French national registry in order to give you a complete idea of the French landscape, I would like to mention that since two years there is a national registry called ---, which is a very active -- it is a prospective collection of medical information only for severe bleeding disorders, and today almost 3,000 patients affected with severe hemophilia A or hemophilia B or Von WIllebrand disease are recorded, and almost 100 patients with severe rare bleeding disorders. Antifibrogenemia, factor II, V,

VII, X, XI, and factor XIII patients are also recorded in this database, which is funded exclusively by the French health authorities and --- go in hospitals to monitor the medical files, and so far 1,300 visits have been performed.

(Slide.)

So two questions may be raised regarding post-licensure data. What is their ability to provide efficacy information, and I will present you our experience in this field, and what is their ability to detect safety problems.

(Slide.)

So regarding efficacy information, before presenting our experience with protein C concentrate, a few words about the product called ---. It is a highly purified concentrate used for 10 years in France. It is manufactured fro the supernatant after cryoprecipitation. There are three anion exchange chromatography steps and an affinity chromatography, and this product undergoes solvent detergent treatment. It is a highly purified product. You can see here its specific activity.

(Slide.)

So we performed a retrospective study in France with a six-year follow-up. In order to identify the patients we performed an investigation among all French hemophilia centers, and we could identify 10 patients. Then 15 recovery

tests could be performed in four patients, and you can see here their status and the number of tests that we could collect. The dose that they received, the PC activity before infusion, after infusion, and recovery values.

(Slide.)

As mentioned this morning, D-dimers is a very good tool to assess the biological evolution of the patient and we could record the D-dimer evolutions in six cases. In one case of neonatal purpura fulminans, in four cases in necrotic purpura, and in one case of venous thrombosis, and you can see the levels of D-dimers before PC infusion and the decrease and normalization of the values and the different times.

(Slide.)

What about the clinical outcome? We could assess 30 courses in these patients, 23 curative and seven prophylaxis. You can see that there is a high rate of response, and the main reason for failure in these four cases where no response could be obtained it was mainly because of late treatment and irreversible lesions were made. I would like also to mention that no side effect, especially no bleeding occurred, even in high-risks situations like surgery or when high doses were used.

(Slide.)

This work has been submitted for publication, and I would like to mention one reviewer's comment saying that we have probably the largest group of patients and the most experience with purified protein C concentrate.

(Slide.)

In parallel I would like to show you our experience with Kaskadil which is the LFB's prothrombinic complex in factor II and factor X deficiency patients. I will remind you the estimated prevalence of these two deficiencies, very rare disease, and we also perform an investigation among French hemophilia centers in order to identify the patients for this prospective trial. No factor II deficiency patient could be identified. It was later confirmed by ---. We could include factor X deficiency patients. We were expecting to include six patients, and later the --- identified six patients, and among these three factor X deficiency patients two of them had a qualitative deficiency.

(Slide.)

Here the study design. It was an open label prospective trial with a unique dose of prothrombinic complex; and in order to have a full pharmaco-kinetics study, 15 samples within 15 days according to the long half-life of the product were planned.

(Slide.)

Here are the results. In the three factor X deficiency patients you can see that hospital tests could show that they had a severe deficiency, and in the central lab test we could confirm this severe deficiency, and we showed that two of them had a --- effect. Here are the dosages. We measure the early end of the curve, half-life, and recovery, but we could obtain only individual values with these few number of patients.

(Slide.)

So I would like comment now sample size issues in prospective trials, in this case of very rare diseases. The prevalence is estimated among the overall population. The diagnosis is performed in all or part of the population, of the affected population. According to inclusion criteria in the protocol, the project is addressed to the available population, which is much smaller than the previous one, and taken into account the constraints of a protocol the participating population is much smaller. So in factor X deficiency according to the estimated prevalence, we could expect 60 patients, but we could include only three, and severe PC deficiency the prevalence is variable according to the publications, but we could expect maybe more patients. We could identify and include 10 patients in a retrospective study. So we can see that even if the items that were

studied are different, this retrospective study was more contributive than a prospective one.

(Slide.)

So what are the specificities of clinical trials in rare diseases?

(Slide.)

The first question is are randomized trials feasible. I would like to remind you here a note for guidance for clinical investigation of factor VIII and IX that is published by the EMEA which recommends to perform to manufacturers an observational study and to include at least 50 pretreated patients treated at least six months or 50 exposure days, to perform 12 cases of pharmaco-kinetics, and to document at least 15 surgical procedures. I would like also to mention in hemophilia A, which is much more frequent that the rare diseases we are talking about, no randomized trial has been performed so far.

(Slide.)

So what is our experience with this note for guidance with factor VIII and IX? We could fit with all the requirements in the European trial, 71 patients. We could perform all the pharmaco-kinetic cases that were requested, surgery we could also do more than was expected. So I think in rare diseases observational studies have to be developed.

(Slide.)

Another question is are clinical trials feasible in healthy volunteers in this field. As we are dealing mainly with replacement therapy, we have to take into account that there can be a thrombogenic risk in infusing a clotting factor in healthy volunteers. There may be an ethical concern to infuse blood products to healthy volunteers, and for instance in France it is not possible to do, so efficacy and immunogenicity can only be assessed in patients. It is not relevant in healthy volunteers.

(Slide.)

What could be the alternative designs to such trials? Comparative cohort designs, and it was mentioned this morning that historical data are difficult to obtain. Case control designs, there are also case control data to obtain. Case crossover designs may be a good option because the same population is studied with a control period, a wash out if possible, and after a treatment period.

(Slide.)

Regarding the second question, I would like to discuss now what is the ability of post-licensure data to detect safety issues, and I would like to present to you our experience with factor XI deficiency with the LFB's factor XI concentrate called Hemo XI. It is a highly-purified factor

XI concentrate. You see here the high specific activity, prepared from the human plasma. The manufacturing process includes a filter absorption and a cation exchange chromatography. You see the high potency, and this product has two viral safety steps, solvent detergent treatment and a 15 nanometer virus filtration.

(Slide.)

This product was used in France at the very beginning in 1992 and very soon after its use activation of coagulation was reported in six patients and even published. So ever quickly the laboratory corrected the manufacturing process and added C1 inhibitor during the manufacturing process, and clinical recommendations were also published. It is very important that the dose should no exceed 30 units per kilo, and subsequent infusion must not be preformed before two or three days, and the physicians have to be very cautious if there are risk factors for thrombosis.

(Slide.)

So after these modifications of the process, we performed followup of temporary utilization authorization, and each time hospitals were requesting for the product we were sending -- sent a form to fill for each patient. So we received 28 request, all batches containing C1 inhibitor, 12 patients received the product, 28 infusions. The majority of

the patients had severe factor XI deficiency, and during this followup neither bleeding event nor DIC were reported. It is important to highlight that the recommendations for use were respected except in two cases where the dosage was too high.

(Slide.)

What about pharmaco-vigilance with this product? Two million units were used since 1994, representing more than 1,000 exposure days, and only one notification of DIC has been performed in an elderly man who received a dose that was one-third higher than the recommended dose. So these two types of post-licensure data confirm the good efficacy and safety record of this product.

(Slide.)

As a conclusion I would say that post-licensure data have a weaker strength of evidence than prospective trials. But they may be a valuable contribution in very rare diseases when prospective trials are very difficult to achieve, and especially if clinical endpoints are addressed and if the exhaustiveness of the population is looked for.

(Slide.)

I would like to highlight the interest for new products to consider the feasibility of prospective international collection of medical information. Both trials and post-licensure data based on an international network to

include patients where they are in developed and emerging countries using common study designs to allow coordinated database and meta-analysis.

(Slide.)

Coming back to the LFB's commitment in rare, very rare diseases, I would say that there is a large part of the portfolio which is dedicated to rare diseases. LFB invests in the development of new or optimized product. You heard a lot about the new fibrinogen concentrate. We are continuously working on the enhancement of viral safety, and the two recent products that received a second viral safety step are antithrombin and the prothrombinic complex, and we didn't speak about IVIG, but we made a lot of work in different rare diseases. Birdshot Uveitis, which is a very rare, severe uveitis; IVIG are very efficient in myasthenia gravis and --- syndrome.

(Slide.)

We are running an exploratory research program in order to perform the purification of new therapeutic proteins. Thank you for your attention.

(Applause.)

DR. JAIN: We can take one or two questions, and then we will probably have a break before the panel discussion. Yes, Dr. Gelmont.

DR. GELMONT: David Gelmont. In the factor XI you had a change in formulation there. You added C1S --- inhibitor. Did you have to repeat toxicology, stability, and preclinical before you were able to use that, or you were granted permission to go straight ahead?

DR. TELLIER: The thrombogenic problem occurred very early. The product was used in 1992 at the beginning, and in the following months these notifications occurred. So it was before LFB was created and before these products had the status of medicinal products. But looking at the file, we can see that there was full toxicological study in animals before and after the modification of the process.

DR. DiMICHELE: Very nice. As part of the International Society of Thrombosis and Hemostasis Working Party on Rare Bleeding Disorders obviously we are very interested in the database that has been established in France, and I would probably say we would be very interested. Right, Flora? Yes, and I was just wondering who is in charge? I mean, who would be contacted if we wanted to have input into an international database from the French experience? Who would be contacted?

DR. TELLIER: There is a steering committee, so it is there is not only one person. The steering committee was chaired from the beginning until last year by Professor ---

who made a lot of work to establish this registry, and the new chair of this steering committee is Dr. --- from ---.

DR. DiMICHELE: From --?

DR. TELLIER: ---.

DR. DiMICHELE: Thank you.

DR. JAIN: Thank you. We can take a 10-minute break and be back here at 3:50.

(Whereupon, a short break was taken.)

DR. JAIN: Okay. Dr. DiMichele is going to now lead the open discussion, panel discussion on this session.

Open Panel Discussion

Donna DiMichele, MD

DR. DiMICHELE: Okay. Can I ask all of the speaker, anybody who is still in the audience?

(Laughter.)

Okay. Now we have the diehards. Those of you, it has come down to this. Okay. So basically one of the things I was asked to do is to actually further engage this panel of great speakers, who have given us a tremendous insight into registries and the issues involved in post-marketing surveillance, and for us to have some further discussions with you all about the relative importance of registries and post-marketing surveillance, the problems, and how we can actually work on both of those systems to help with the

ultimate process of getting products licensed for rare bleeding disorders. That is the focus that I would like to have right now in terms of this discussion.

Let's see here. Okay. Yes, I think we lost the video signal, so while we are doing that I put together a few thoughts that I would like to kind of -- I was going to show, but maybe I can just read -- I am putting them to sleep already -- to basically get the discussion going.

(Working on equipment.)

I have sort of titled these comments registries and post-marketing surveillance. You guys can't see it up there. I am sorry, so I will read it to you.

(Slide.)

I think that we have identified that there is a role for both. I think the question is whether both are one in the same, and one of the questions that I would like to pose to the group that remains, the panel and the group, is, you know, what is the role of registries ad what will be the role of post-marketing surveillance in this whole process. One of the things that I would like to propose is that registries may be a pretrial tool, but the question is can they also be used in the post-marketing surveillance manner as well.

Now, I think in this sort of day of talks we have

identified the registries as being important with respect to several issues that might help industry, might help the FDA, might help the investigators get through their trials. One is identifying patients with rare disorders in general. Also providing natural history of disease data as well as historical treatment data, both of which -- all three of which, have been identified as being very important in sort of getting a clinical trial on therapy for rare bleeding disorders or rare disorders in general going.

It seems to me, and again the panel members should comment on this, that those companies that have attempted to do this have spent a fair amount of time gathering this information together, sometimes successfully, sometimes unsuccessfully, and the question is whether registries for rare disorders might obviate some of the difficulty that individuals have had. So if we agree with that, then the question becomes how do we establish these registries, who has the jurisdiction, are these industry-sponsored events, are they national databases, are they international databases, how are they managed, who has access to these data, how can they be used optimal, obviously what do they contain, and importantly how they funded. Also importantly if we really want widespread participation is how do we simplify the IRB or the ethical committee processes to get

these registries included in most of the centers that would be collecting this data, because this now becomes a major issues that we have to contend with, and simplifying the process is something we may want to discuss as part of our discussions.

(Slide.)

Now in terms of the post-marketing surveillance, the question is has that more of a role post-trial; and certainly some of the issues regarding post-marketing surveillance and the importance of post-marketing surveillance has been again illustrated by many of the speakers today. Including the potential simplification of trial design and creating an actual pre-licensure clinical trial design that is more focused on what we need rather than what we want by allowing us to get maybe some more of the data about what we want in a post-licensure way, expediting trial completion by relegating some of the extraneous information, important but extraneous information, to a post-marketing sort of time frame. Gathering more data and doing that by gathering more data on efficacy, basically correlating surrogate endpoints that might be used in a clinical trial ultimately with clinical endpoints and certainly collecting relevant safety data. All of this has been actually discussed by a lot of our discussants today,

and I think we can sort of see where we might want to go with that information.

Then finally one of the most important roles of post-marketing surveillance is that it appears to be a model for EMEA and FDA harmonization, and there has certainly been some work done already in potentially harmonizing that aspect of the process. The question is how do we capitalize on that.

(Slide.)

So if we think that post-marketing surveillance is important, then the question becomes, okay, how do we optimize the process? How do we make it more compliant from, you know, industry all the way down to individual centers, individual investigators, and participating subjects? Ultimately some of the questions that I see that need to be discussed are whose responsibility is post-marketing surveillance, who is responsible for the design, the execution, and again the funding of these endeavors, and how can compliance be encouraged? Should they be voluntary versus non-voluntary? And one of the things I would like to see discussed is that I know that there is some ongoing work and certainly some ongoing push to have post-marketing surveillance occur at the time of license application, but what would happen if post-marketing surveillance and the

post-marketing surveillance study was actually part of the original clinical trial design? Such that, for instance, all the centers that would be participating would have one IRB application that would include clinical trial design and post-marketing surveillance. Might that really help with compliance? And once we get that data, how does that interface back eventually to the ongoing disease registry that might have started this whole process? So with that initiation, I would just maybe open it up to -- yes.

MR. : ---. (Away from mic.)

DR. DiMICHELE: Oh, that is right, we are missing -- just when you thought you could relax.

(Laughter.)

DR. DiMICHELE: Okay. So with the panel now assembled, I don't know if anybody wants to initiate any comment with respect to any of this. Maybe we could talk about -- yes, go ahead, please.

DR. TELLIER: Yes. I would like to make a comment regarding the partnerships and who could be responsible for PMS and also the constraints. In France there is this institutional registry I mentioned earlier and PMS sponsored by companies. The clinicians felt very upset sometimes to collect the same information many times, and they feel that there is a misuse of their time and energy mentioning in

different forms the same information. I feel that there is a strong request from them to have a single database or at least a single collection of information in order to save time and not have this redundant activity.

DR. DiMICHELE: So for instance in the French model then would since the registry function is actually funded by the national government, would you propose that they also fund the post-marketing surveillance then that ends up being the same tool? Or how do you begin to separate those functions and those responsibilities?

DR. TELLIER: I think that I can understand that it is very important that registries are independent, but I think that it is compatible with different partnerships in order to share information to save the independency of the databases, but also to avoid -- because it is also a constraint for PMS from laboratories because some clinicians have -- there is a reluctancy to include patients because they don't have the availability to fill all the forms they have to fill. So I think that we can foresee discussions in order to preserve independence and also to share information.

DR. DiMICHELE: Yes, and it would be interesting and I don't know whether industry would like to comment on this as well, because I know that there have been issues in the past when we have tried to collect data, let's say in

immune tolerance in a registry format, and yet for instance some of the immune tolerance is being done as part of clinical trials and really separating and having some discussions with the companies about what data they need, you know, versus the data that would come back to the registry. It becomes a little difficult sometimes in terms of maintaining that jurisdiction, but I think it is important. I agree with you, I don't think people will fill out two sets of data. But maybe with electronic data now some of these data, it is easy to send these data to two different places, and maybe something could be worked out. Mike, did you want to comment?

DR. SOUCIE; Yes. We have heard a lot today about registries, and it is sort of one of my peeves is that really that word is really in many cases sort of overused or at least imprecisely used, and it is many things to different people. It develops and, you know, a registry can just be something that, you know, any patient can just sign onto and say "I'm here." Or it can be, you know, all the way up to something, you know, that have been described, some of the systems that have been described here that have been, you know, very useful in terms of doing this kind of surveillance.

So I guess, you know, what I would like to propose,

and that is sort of the notion that we have with the data collection system that we have set up is really to think of it as sort of a national database. I think that, you know, what Flora has talked about for rare bleeding disorders is sort of this framework of a database, you know, international as it might be or national and maybe linked, it provides a structure or a framework that you can, you know, maybe address some of the issues that we heard here that we heard about all day yesterday about, you know, how expensive it is to identify these patients, to get them together, to administer, to be able to follow their complications, their care, and so on. But it would be so much simpler if all these patients were already identified in a national registry or here I use the word again, international database, which could then as you -- I think it is an excellent idea to be thinking as especially with these rare disease as you are designing a study, is to consider all phases of it. Which includes if you are going to, you know, use the accelerated, you know you are going to have some post-marketing commitments, and so why not plan for those up front.

If you have a registry that already has patients identified, it makes since, seems to me to make sense and really sort of simplify the process all the way through. Those are just some general idea, but if we could just sort

of think of it in terms of databases as opposed to registries, which some people have different ideas of what a registry might be. I think everyone can sort of agree to what a database might be.

DR. DiMICHELE: Then all we have to figure out is who gets the data.

DR. SOUCIE: Those are the issues, and I think that comes back to Dr. Tellier -- my French is non-existent -- in pointing out that certainly I think that there is a tendency for most people to feel like, you know, a government or some kind of independent database that is not -- clearly not identified with any one manufacturer. Those kinds of issues are certainly preferable to, you know, other things.

DR. DiMICHELE: And I think we have some industry responses. Dr. Ewingstein*?

DR. EWINGSTEIN*: Okay. So I think that Mike is right. I mean, we are talking about a lot of different things with a lot of different people, but I think in the setting that we were sort of here to discuss I think that the issue of having a post-marketing surveillance program as a way of substituting for another prospective trial I think is something that would be helpful, okay, in terms of getting products that may have had good PK data and only a limited amount of actual efficacy data and safety data collected and

then move into this form. But in that setting I think that particular study should be very directed around the product. The form, I agree with your point that it could be considered part of the overall regulatory strategy from the beginning.

I think the regulatory agencies would have to tell us what data they would feel secure in having in terms of safety data, and I think that it would have to be conducted at a certain level that would at least guarantee at least a certain level of data integrity. So you have a registration study, you know, you are doing very intense monitoring, verification of, you know, primary source data, et cetera. So I think you have to sort of think about, you know, some intense period that could be a year, two years, even five years, where a particular product would be studied in a particular disease. Perhaps not with the same monitoring and scrutiny as a prospective study that we are traditionally talking about, but still in a different way than a registry. I think the registry idea is great for sort of studying the long-term natural history, you know, for having a database where sponsors can go to find patients quickly, where patients on different products can be sort of combined in a way that is not unique to a particular company's point of view.

But I think that we are talking about here is

something between a registry and a full-blown prospective clinical trial with 100 percent monitoring of source data, and I think if we could sort of think about -- maybe the regulatory agencies could, you know, sort of speak up on what would satisfy from their perspective, you know, a credible level of data integrity.

DR. DiMICHELE: And then there could potentially be re-importation back into a national database. Maybe what I will do is there are two other individuals from industry who wanted some input into this, and then maybe we will ask regulatory to potential comment from both sides. I think Mr. Turner and then ---.

MR. TURNER: Yes. Thank you. Look, just to reinforce Bruce's words, I think industry has always invested a lot of money from this time. So they will want to have some sort of overview of where this is all going, and data integrity is a huge issue as far as the companies would be concerned. You know, you get reports back on products which, you know, sometimes are said to be, if you like, clinical events, adverse events that are product-related that turn out to be nothing to do with the product. So I kind of feel if you are going down this path how it is all set up is pretty important. I have no issue with the data being used in registries in the long-term, et cetera, but I think the

companies who probably have to fund these studies will probably want to have a reasonable amount of control over how they are done.

DR. DiMICHELE: A very good point. Dr. Dash?

DR. DASH: Yes. Clive Dash, IPFA and BPL. I think the three of us are thinking along exactly the same lines, but I would like to rephrase my comments as slightly differently and reinforce something that is happening in front. We have heard about PMS. We have heard about PMC. We have heard about pharmaco-vigilance plans. We have heard about registries. We have heard about lots of things. The question that I would phrase is where along that spectrum do we invoke GCP and where do we not invoke GCP? Where do we go for straightforward audit, and where do we don't go for straightforward audit? It seems to me that somewhere we have to draw a line, and I think the two previous contributors to the discussion have said more or less the same thing. I think one of the strengths of the French system is what was said by Dr. Tellier in her presentation, was that -- if I remember it correctly, was that the French government sponsors or pays for CRAs to go into the individual centers and validate the data that is being collected into the French registry. I thing that is an enormous amount of strength and validity to the data in that registry.

DR. DiMICHELE: All right. You make a good point. So does it -- Dr. Seitz, would you like to comment on the regulator's view of the discussion up until now? And I don't know if somebody from the FDA would like to as well.

DR. SEITZ: Maybe a few remarks. First of all, I think it is very important that we come to consensus about objectives of such registries, and it is very interesting to hear from the industry. Well, this may be a good source for recruiting patients of course, and this may be a way to find out which parameters are important for the regulatory agencies. Regulatory agencies of course have their own dreams. They dream of being able to license products with limited data and then have some assurance from the registry that nothing happens undetected. Of course the scientists have their own dreams about knowing more of the disease and providing better care for the patients.

But I think we have to be carefully that we really figure out what we want to have, because at the end the crucial thing is that the patients are giving their consent to be included in such registries. At the end it must be very clear for the patients what they are giving away and what do they get for it. For instance, if we would have the ideal case that we would have a registry including all the patients with a certain disease, and if a company wants to do

a study with these patients, then they would recruit some patients from the registry. Now we talk about data integrity. During the time they are in your study, do they still contribute their data to the public database or are these data then excluded and the patients have to go out of the registry for a time and so on? That is just one aspect, but the difficulties are always in the details.

Maybe another, in your slide you have voluntary versus non-voluntary. That is an interesting phrase. I would say as it comes to the patients you certain cannot have any non-voluntary recruitment of patients for such a registry. Of course this has to be from the patients' side voluntary. You cannot force anyone to give away his data for a registry.

Maybe with the treaters it would be a little bit different thing. You could say, well, if you are a treater who has a quality control system and really you work state of the art, then you have to have a good documentation and you have to participate in such registries. Actually in Germany, the health insurances are a little bit thinking this way. So you get your full payment only if you have a really quality system and this includes documentation. That might be another aspect.

So at the end I think we as European regulators are

quite positive with our registries, but it really depends on the details. It is not so easy, and it will be a lot of work to come to consensus, to come to mutual trust, mutual confidence, and I think most importantly to convince the patients at the end it is something good for them.

DR. DiMICHELE: Which I think can be done, and I agree with you the dialogue is going to be most important, but sounds like we are developing the mechanisms to continue that dialogue on a multilateral level. Dr. Braun from the FDA perspective.

DR. BRAUN: One of the FDA perspectives. I think it is illuminating that Dr. Soucie that is working with something that might be called a registry admits to some uncertainty about the terminology. I noted in my talk with the ICH guidance there actually is an annex that talks about different terms and tries to define them, and I believe registry is one of them. I think, you know, as this field focuses on this area we need a more granular terminology and where people can communicate more clearly on these kind of issues.

Registry can be people -- well, the way we dealt with it in the FDA guidance, is you could define a registry based on a disease. So one of the rare plasma disorders certainly could have a cohort of patients, but we also have,

you know, when we have licensed new vaccines we had a pregnancy registry -- well, not we, FDA, but the sponsor will have a pregnancy registry of people who are exposed, women who are vaccinated during pregnancy or right before. So that is not really the disease of interest; it is the outcome. There are liver failure registries. Liver failure as adverse event from drugs, not as an indication for a product. So, you know, we need to be precise about, you know, what we are registering. You could have a registry of HIV patients who had HIV through blood; so, you know, you have to -- what are we talking about in terms of a registry, and all of these registries, and so we said this also --- have a protocol. So this idea and the term registry is used this way. You have got to have a registry of patients with rare disorder X.

Well, you know, what we are saying, and this is good pharmaco-epidemiologic practice, would be to have a protocol when you embark on this effort. So it really in a sense becomes a study at that point. So there is some kind of study, you are asking a question, or you at least have a protocol. You know, then there are many different study designs. You know, we can have cohort studies, so you can have the prospective cohort study of people with a rare plasma disorder treated with product, and I think is somewhat what we heard about today. But there are other study

designs, too. Case control studies, which are very different from that, and so that is why I say in a way it kind of helps to specify what we are talking about.

Post-marketing surveillance is a requirement of the regulations in Europe and the United States, so that is spelled out in the regulations. But what is beyond that, and that is what I think we are really talking about here, is pharmaco-epidemiologic studies, observational studies. It is a challenge when you have a very rare disease where in a certain way someone could corner the market, you know, to use the business sense, on a small group of people, and then I could understand the concern about who actually had the corner and whether it was -- and that may be a time where one can try to justify government involvement and it becomes appropriate because it might not be fair or right if one interest had a corner.

So, you know, those are some of the things I think that -- I will just close by saying this area of work, you know, has been developed in other -- in the drug area and other biologics, and many of the concepts and the principles do apply. I think there are some special issues that affect rare diseases and those need attention, but I think it is helpful to borrow a lot of the work that has been done in other related disease areas and product areas.

DR. DiMICHELE: Thank you both for those comments about regulatory. Yes, Dr. Scotland.

DR. SCOTLAND: Yes, this is Dick Scotland. If I could, just a couple of comments. The value of a registry to me is the ability to identify patients as quickly as possible to be able to enable enrollment. In regard to immunological assessment, I would just like to comment that from my perspective anyway the value in that is if you have a treatment where you only -- a treatment for a condition where you only treat these patients very infrequently and you want to capture data on safety of retreatment over a long period of time, there is some value in that provided that you have at least a baseline sample prior to the second treatment or third treatment or whatever else, and then -- so in other words, if you don't have a baseline value it is very difficult to interpret the data. Thirdly, on terms of patient registries or data registries, typically with any kind of clinical trial you prospectively state how you are going to handle missing data, and so there may be some ways you have to think about what to do with missing data. You can either extrapolate or you can just reject the patient; or if an investigator is being paid or incentivized to put information in, you can have a followup mechanism where you can try to prod the investigator to provide the information.

DR. DiMICHELE: Very good. Do we have a comment on that from anyone in the panel? Dr. Casper.

DR. CASPER: I think in acknowledging Dick Scotland's remark I was very interested in the role of registries to accumulate historical -- semi-historical data on rare disorders, because certainly common disorders would be too massive an amount of work. I think that deserves some function. That deserves some thought, because some of this is in charts and charts are sometimes destroyed by hospitals after a period of time. That is becoming common practice. They just disappear. Older clinicians who might know where on the chart to look are retiring. Bye, all. I think this is a good function. What I think I hear people saying about all this data collection is that the clinicians who could probably do it efficiently because they may know where to look for the data or whoever knows where to look, they have an awful lot of stuff to do, and I don't even know whether funding them would be enough. But some kind of funding for that kind of service of not only keep the registry in its central location, but as you are trying with the hemophilia research, the Hemophilia and Thrombosis Research Society, to fund the collection of historical data for those disorders where you need it on the local scene.

DR. DiMICHELE: Very good. I mean, so what we are

hearing so far is that certain the issue of registries needs to be clarified in a major way and that these databases need to be defined with respect to their function. Most likely protocol-driven as you have mentioned, and potentially tiered. I mean, you know, so what we might be talking about for instance if we are looking at rare bleeding disorders is we are looking at epidemiological databases, and we are looking at genotype databases, and we are looking at natural history databases with respect to bleeding, and we are looking at treatment databases and complication databases, all potentially coming from the same source and being contributed to by the same subjects. But nonetheless, very separate databases that are there for their own right and certainly from a scientific perspective to document data that is very, very important to document in and of its own right. But potentially could serve other purposes such as, and this very important purpose that we are talking about today, such as, you know, databases to initiate the very thing that we are all here to discuss today, and that is proper, you know, treatment and treatment trials by virtue of just cutting some very important steps out of some processes instead of taking a lot of time and a lot of effort and a lot of money so that the money can be put -- nobody is talking about taking away the money, but the money can then be put toward other things

such as, you know, in the cost effectiveness or in the cost profiling that industry has to do. The money can be spent in other ways, including the potential for post-marketing surveillance and maybe, you know, these projects wouldn't be scuttled right up front because of the time and effort and the money that is perceived and actually just even defining the database of patients.

Then just one more thing. Then what I am also hearing is the issue of potentially post-marketing surveillance studies for specific products may be needing to be kept separate, but potentially then that data can be able to be re-entered back into ongoing databases. For instance, treatment databases in that way, and then the data being sort of, you know, being able to be transferable in some way. But specifically owned by industry for the purposes that are going to require, you know, their fulfillment of their post-licensure agreements with regulatory bodies. Anyway, that is what I am hearing so far, but -- Jay.

MR. EPSTEIN: Thanks, Donna. I just wanted to make two comments. One is just if we naively assume that databases or registries of some sort will be valuable for rare blood disorders, and I think we have already seen evidence that aggregating these databases has a tremendous value. Because in any one region the numbers are small, and

if you can get to national aggregation you get a much better picture, and if you get to international aggregation it is better yet, and I think Flora's presentation showed us in very stark terms that the current state of play is quite a lot of independent efforts that are really not coordinated. It takes work to pull things together, but that it offers a lot of return.

So I am just wondering if we can get some comment on where we see the forum to bring things together. Is ISTH the forum? Should WHO be playing a role? What about World Federation of Hemophilia? Should it be disease by disease? Would it not be better to look at rare blood disorders as a whole? So that is my first point.

The second point -- I am going to give people a chance to think. My second point is really a message for our industry partners, which is that I don't think that as a regulator it is possible to simply provide a statement of how we would trade off our registry data, either historical, prospective, or post-market surveillance data, against pre-market studies in general. The reason is that the different disorders have their own unique character. The quality of the historical database varies quite a lot. The assessability to the patients varies quite a lot. The suitability or lack of suitability of controls in prospective

trials, et cetera.

So I think that the message that we need to send is that we invite the manufacturers to come speak to the agency one-on-one so that we can have a meaningful dialogue on the barriers to development and they are perceived by candidate product sponsors and can deal then in that, you know, confidential environment with the entire question of how we would design the approach to eventual product approval. I think that we have been trying to send the message that we are open-minded, that we have many tools at hand. You know, there are the financial incentives that were discussed with the small business grants. You know, there is the Orphan Drug Act. There are other ways that one can try to leverage for example common controls in multiple studies. There are lots of things that we can do, and I think that the one barrier that we want to remove is the concept that we are not willing to listen to new ideas. We are, and we are prepared to be flexible because we do want to see progress in this area responsive to, you know, the patient and the public health need and demand.

So the only other point that I would add is our goal is we are not a thing apart. You know, we are a reflection of our society and its priorities, and our -- what we seek is to be scientifically state of the art. So, you

know, we very much need the input and clear thinking of experts in making any of these kinds of tradeoffs that are being described. It is not a thing that can be done in isolation, and there really wasn't a lot of elaboration about what happened with advisory committee process in Fabry disease, but I think anyone that is familiar with FDA understands that this is our paradigm that we would take things to public discussion, that we would seek to be advised by experts. So if we could come back and perhaps just ask the panelists what they think about database integration internationally I would appreciate it.

DR. DiMICHELE: Well, I would like them to comment on that. But before we do, I just want to just clarify something though. Because yes, indeed, you know, I think your statements about where the FDA stands on this are very important, but I think would you agree that with the premise that we are discussing right now in terms of this panel that the issue of databases, ongoing databases for -- disease-based databases, whether they are an aggregate, whether they are national, international, you know, and that discussion needs to be had, as well as post-marketing surveillance has the potential to simplify the clinical trial process to get products to market for rare bleeding disorders. I mean, would you agree? I mean, this has been a large part of the

discussion in terms of how all this can be facilitated in a way that it is not being facilitated now, or certainly there is an appearance that it is not being facilitated now. Would you agree with that premise? I mean, I don't want to put you on the spot, but I mean -- but I kind of am, and I am sorry about that. But I mean, you know, I think we really need sort of a ground. You know, some sort of a framework for moving forward I think, and I am trying to establish that.

MR. EPSTEIN: I think that what I have been struck by is the European framework and the US framework are really quite similar. We have some different terminologies. You know, you have the marketing approval under the exception provisions in the law, and we have accelerated approval which does essentially the same thing. In both instances post-marketing studies are required and they are oriented toward demonstrating the actual clinical benefit.

At least in the French law you have the ATU, and in the US system we have the treatment IND as well as the convention IND and the compassionate use IND. So we do have the capability to progress along the kind of paradigm that Keith Hoots outlined, which is sort of all the parts put together linearly, and I think that we have a handful of examples where we have actually done this. I think that the challenge is to figure out in which instances the model fits

best, and I don't think that we can give a generic answer except to say that we are willing to consider the applicability of registries and, you know, retrospective historical databases and post-marketing studies to condition the preapproval requirement.

We do have an open mind on this point. It is just that I think that in any given instance we have to have a discussion on the merits. That is all I am saying, so I think that I don't have any resistance in concept. I don't think that my colleagues do either, and, you know, we could perhaps have cited the FDA examples instead of the worldwide examples, but there are some. I mean, just to give you one, in the case of immune globulin intravenous for primary immune deficiency. We did put forward a model which we discussed in advisory committee of a small prospective trial modeled against a statistically-modeled historic control, and that enabled us to do a very small trial to reach what we felt was a hard clinical endpoint, which is number of serious infections per annum, per patient per annum. So, you know, we have taken steps in this direction. What I am not prepared to say is that this is the new answer for all cases, because I think we have to look at each case. But I think it is a very potent tool and that we are interested in making the maximum use of it.

DR. DiMICHELE: Fair enough. Okay. Shall we discuss the database issue? Yes? Oh, okay. Sorry. Dr. Seitz.

DR. SEITZ: Just one remark onto what Jay said. You are right, we are quite similar, but there is a little difference. Maybe it has not become clear enough. You have the accelerated licensing and we have two mechanisms. One is the exceptional licensing and one is the conditional licensing. It is a little bit complicated in as far as I understand the conditional licensing in Europe corresponds to what you call accelerated licensing; and the point is that you want to have a product on the market and you know that the dossier is not yet complete, but you expect at a certain point of time the dossier will be compete and there is a program that then can be done after licensing to get one day a complete dossier. Bu the exceptional licensing is really that the condition is so rare that we cannot expect to have ever really a complete dossier and a complete assurance of efficacy and safety from these studies. In this case I think it is a little bit different. In this case we really want to have everything we can from the post-licensing period to be at least assured that we will not overlook problems in the future. Maybe that is a slight different between our systems.

DR. DiMICHELE: Okay. Flora and Tom.

DR. PEYVANDI: I think first of all I wanted to underline something that I am very happy, because just two years ago all of us were working on the rare bleeding disorders in our house, in our nation, but none of us could even share the data together. But now at least we can sit down here and make the question that Donna was mentioning. To be completely honest, in these years I was trying to answer the question, but I don't think so there is any answer to all these questions, and the answer has to come up from this room. So we have to make some type of agreement together with different aspects and the different groups, clinicians and the regulatory people, from the States, from Europe, and industry, and to make the representative of each region of the world in getting some type of agreement together how we want to treat. Because the most important problem is the property of the data. This is the best -- I mean, this is the only question to my opinion, because everybody is making some type of registry, and they think this registry belonging to them. Once we resolve the problem, this data is not belonging to none of us. It is only international or national, whatever it is, and it could be shared for all the different groups. Then we have it solved. But the way to arrive to this conclusion I think is

not so easy.

DR. DiMICHELE: Flora, one of the questions that was asked was do we think that -- well, one of the questions that was asked was could this be an ISTH, factor VIII, factor IX subcommittee, you know, working party, rare bleeding disorders working party, could this be sort of a mechanism. Now this would be specifically rare bleeding disorders, so it is not all rare protein disorders. But could this be a mechanism and could other subcommittees, for instance in the ISTH, take up the model of, you know, products for rare thrombotic disorders, et cetera. So should the ISTH do this? Should the World Health Organization do this? And I don't know if --- wants to comment as well, but what is your comment on that?

DR. PEYVANDI: I mean once we started to work on the international registry of course I immediately got in touch with the ISTH because I was thinking this was the best way to understand how we can, you know, have an international registry. But to my feeling, I mean, both World Federation of Hemophilia and ISTH, they are very happy to collaborate. But I think there is no organization still established how we want to do that. That is the reason I think we have to resolve the problem and we have to answer this question. I think we have to do it through the international society. We

cannot as a single group to work on it, but still what means the International Society of Thrombosis and Hemostasis? That means we have to choose some steering committee, and this steering committee has been choose with who? Who has the authority to choose who is responsible for this registry? But for the starting I think absolutely we have to start with World Federation of Hemophilia and ISTH. There is no doubt about that.

DR. DiMICHELE: Tom.

DR. ABSHIRE: To answer Jay's specific question about this aspect of an international registry, I think first you have to start with each national has to get their act together, and I was mentioning before at the break that in the US we are more like medieval Europe than Europe. We have a bunch of little individual fiefdoms and silos that coexist apart from everyone else, and at least you have heard from the discussion from Dr. Soucie and I that we really have great hope that this is going to change within the year. I think we have to start there, that the nations have to get organized so that you have a database, you have everyone at the party, at the table. You are designing what information to collect, and then you can talk to other groups about how you are going to get together.

The second point is that I believe that since we

are all open to new ideas, if we did have a database that was properly managed and monitored, I think that the paradigm could shift in terms of how we collect data. I would like to give for example the oncology groups exist in all the different countries represented here where I don't think anyone would disagree that these are peer-driven organizations. The data is rigorously monitored. There are phase I trials that go on through these organizations that lead to FDA and EMEA approval and they are monitored. So these are organizations that grew out of the infancy and then developed a very good life of their own, which I think would be a good model for us to follow.

For example, you don't have every institution within the Children's Oncology Group monitored every year for the accuracy of their data, but they are site-visited at certain points in time to look at the accuracy of the data. So we could consider that from the concerns that were raised earlier from government, and in terms of how the data is collected, you know, there is a national statistical center of national data. Then when you have things happening at the national level then you can interact with people at the international level, and I agree with you that this should be part of, you know, ISTH as the scientific aspect of what we do.

DR. DiMICHELE: And if I could just add, I think it has always been thought that national databases would be maintained and feed into an international database, and that I know has always been Flora's goal to also establish databases in emerging countries, and that is where the World Federation of Hemophilia comes in where most of these patients are, and yet they have the least capacity to actually collect the data. Obviously the data from those countries is extremely important and collecting good data from those countries is extremely important as well.

Dr. Seitz, I know you had a comment, and then --

DR. SEITZ: Just another comment. I was puzzled by some remarks of Dr. Casper. I think that, okay, we want to collect historical data, and on your slides you asked is it pre-study or post-study. I think that is not the right view. I think if we embark on registries we give birth to something that will be living. You know? Not only on one point of time before a study or after a study. It will be a prospective collection of data and it will be in parallel to studies. It will be a new entity which will have their own life, and even not only one registry. There are a lot of registries around as we have seen today, and important to make sure that these registries can talk to each other, and can have a dialogue and can produce data which are available

for all of us. But coming back to Jay's comment, I think it will not be a tradeoff of studies against registries. There will be two things in parallel and there will be not at all a tradeoff, just to make that clear.

DR. DiMICHELE: And let me clarify since I made the statement. There was no way that I really felt that the registries were going to be something that would be borne to just help clinical trials and then just sort of die off. Obviously they are entities in and of themselves, but I was looking at then as to how they could help in this clinical trial process, in this licensing process, in this -- you know, in making treatment available process. I think that is where I was focusing, but absolutely. I mean, I couldn't agree with you more. Dr. Bergman.

DR. BERGMAN: Thanks. Yes, I had two comments. First, I think as long as a company has a product that has been approved with less than a full dossier and they have commitments to regulatory, I for one would be reluctant to relinquish control of collecting that data in a way that I knew that it would be accurate and complete, and I would not want it shared publicly until it had been collected in toto and evaluated in toto. At the end of that time, having presented it and had it reviewed by regulatory and a decision made, yes, it is enough, no, it is not enough, then it would

be released more or less for placement on a registry. There are several reasons for that just anecdotally. Early in the development of one of the products that I was involved in developing, 10 or 15 years ago, we had a nine-month old pup who developed an inhibitor with anaphylaxis, and it was only the third or fourth or so patient involved. If that had hit the press we may never have finished that study and may never have gotten that product out, but it didn't. It was in among the investigators it was known, among the IRBs it was known. Okay? So at the end of the study when it was all said and done we could put that in context, and I could see where something like that could happen in a post-marketing surveillance as well. I don't like the term post-marketing surveillance. To me that means something less than accurate verification of data, and I think that is an important distinction to make. I am talking about a prospective collection of verified data. Okay?

The other thing is as I was looking around I was thinking of all the international databases that are being put together. I don't see any representation from Canada here, and I think they probably have one of the best. The Association of Hemophilia Directors of Canada have for the last half dozen years an excellent database on every single patient, where they are, what they have been treated with,

how many have inhibitors, what their inhibitors are being treated with, and they share it just among themselves. From that database they have already published a couple of papers, and so I think that would be a really good thing to be included.

DR. DiMICHELE: Well, as a Canadian myself of course we wouldn't slight Canada. But, and as a matter of fact, they are very much involved in this process, and just to reiterate the collection of data that went on, you know, the published data that came out of here, was North American. It involved Canada and the United States, and they have gone on to develop their own registry of rare bleeding disorders; and we have been in touch with them when we have been trying to actually develop a collaborative data base, so the are definitely very much involved.

MR. : --- (Away from mic.)

DR. DiMICHELE: There we go. We would never exclude them. Absolutely. Dr. Soucie. Excuse me, before you go, I just wanted to make a comment. I understand exactly what you are saying, and I think the way sort of this concept is evolving the post-marketing collection or verification of data would indeed be, you know, potentially an industry-sponsored function. But in its ability to eventually transfer back to an ongoing data collection it

would also be able to limit the amount of time in which, you know, industry might be responsible for the data collection. Then it would revert back to certainly a national database, and clinicians would then have responsibility for that ongoing surveillance. It certainly could develop into a partnership, and I think that is what we were assuming. So I don't think anybody was assuming that there would be sharing of that data until -- if industry did have control of it, until it was ready to be shared. That is at least from my perspective.

DR. BERGMAN: Yes, that is exactly what I was thinking, and it certainly brought to mind things that we have read in the papers over the last six months about pharmaceutical companies that don't share all their data.

DR. DiMICHELE: I know. It is terrible. Dr. Soucie, I don't know if you wanted to comment on that first, or you had a totally different -- okay.

DR. SEITZ: I just have to say we have to be careful before we take any decisions like that. I think that is a point we really should think about. When does a patient belong to a company for a study, and when does he go back to the registry. That is a very delicate thing.

DR. DiMICHELE: No, and certainly no decisions are being made. But we are just sort of bringing out ideas here.

I mean, and I think we are trying to develop a framework for potential, you know, sort of collaborative effort that sort of meets a lot of different goals I think. Mike -- but in no way do I mean that we are sort of setting anything that regulatory would have to abide by.

DR. SOUCIE: I guess I am not really sure how to say this, but there is a big difference. I am sure everyone in this room knows this, or at least relatively sure everyone knows this. There is a difference between a clinical trial and surveillance. I mean, everyone knows that, and the reason that we are talking about using a surveillance system, which is typically not set up like a clinical trial, you don't have patients that you see on a regular basis. You don't have measurements all tied up in a row. You don't have a patient agreeing to come every week for 10 weeks to do this process. What we are talking about is using a system that we have used for -- you know, that we have set up for blood safety monitoring for example just to use my own. I am not speaking for anybody else here, but to use that structure and sort of the efficiencies, and also because it is not so intense and because you are not collecting so much data, you have a lot more access to a lot more numbers of people.

While the data may not be as frequent as you would like and that you could set up in a clinical trial, if the

idea, the notion is that if you extended and you did enough to enough people that you -- there would be possibilities for you to be able to do things that you can't do in a setting where you have to have all these rigorous guidelines and so on.

I guess that is the reality. I would like for industry in particular to keep that in mind, that I think what at least clearly what we are talking about doing is using a system to get more data on a population that is otherwise as everyone has recognized here is extremely expensive and extremely hard to get at, but you try to get at by a different way. I just would like to throw that into the mix because I am not sure that it is really a realistic expectation of industry to consider that a surveillance system is going to have the same rigor in terms of, you know, all the detail of study design and so on that a clinical trial does. That is why it is not as expensive, and that is why we are even talking about it. And again, I am not trying to bring down the possibilities of a surveillance system, but it is important that everyone understand that is why we are talking about doing it. It can't be as rigid, otherwise you would have a clinical trial.

DR. TELLIER: Yes. I would like to mention that post-surveillance studies bring useful information because we

are in the real conditions of medical practice and not in the theoretical scope of clinical trials, and sometimes this condition of very practical, routine medical practices are very complementary to clinical trials. I also would like to say that it seems to me that there are two kinds of registries. Registries which are aimed to diagnoses and all the patients are recorded in these databases, and other registries which are more aimed at treatment, and I think that the French national registry includes only severe bleeding patients who are the first candidates for treatment. So I think that there two different scopes, and maybe the future some guidelines for establishing registries may be useful and help distinguish the objectives and trying also to make a different registry able to talk one to each other if they are precisely defined.

DR. WEINSTEIN: Just because people have to go very, very soon I just want to have comment here as one potential outcome that we could agree on perhaps at this meeting would be just to simply establish a hyperlink between various databases that have been formed so that people when they contact one database might know that there are others in existence that are of somewhat of the same nature here so they could at least access and have some idea that these other things exist. What they do with it and how it turns

out is another question, but I think that could happen. Do you agree or not? Is there some impediment that you see to that notion? That simply if you get onto the UDU one that you will know that another database is being developed by PI or that is available in France to look at for this patient population. I don't know if such a thing exists now --

DR. DiMICHELE: No, but that could be a function of for instance of ISTH and the international database. That would have all the component national databases so that -- yeah.

MR. : Can I make one --

DR. DiMICHELE: Hang on one second. I don't know if you want to end this part. I mean, part of my panel is leaving, so I don't know if you want to end this part of the discussion and move on to your part of the -- yeah, exactly, your part of the discussion. But go ahead, Dr. ---.

DR. : Yes, I would like to make one final comment on the issue of the ISTH commitment and perhaps it is useful to remind you that a working group was initiated by Professor Manucci* and has been amply discussed in the SSC and --- for the time being in the factor IX/VIII subcommittee. So we already passed the point of no return. There is full commitment by ISTH and I would encourage anyone in the audience to do his or her very best to provide data to

---, and the reason, well, there might be some overlap as other ---, other subcommittees. But the reason for the ISTH to place this in the factor IX/VIII subcommittee is that that subcommittee is the one that was the most experienced in bringing products to the market and making them available. Of course, that is the second message of this working group.

DR. DiMICHELE: Good point. Very good point. Well, I am going to thank our panel for a very interesting discussion and obviously the basis for a lot of ongoing discussion I think. Thank you very much.

(Applause.)

Panel Discussion: Where Do We Go From Here?

Mark Weinstein, PhD, Session Chair

DR. WEINSTEIN: So we come to the end of this workshop, and for our last panel discussion the question is, "Where do we go from here?" I put various names here on the table here, but actually you are all a part of this final discussion, and we look forward to having an interchange of ideas about what to do next. I included Mary Gustafson on this panel as a representative of PPTA and the foremost question I think at the end of the day is, is this helpful to industry? Has this workshop facilitated the process? This is what we are looking for at the end, to facilitate the process of rare plasma protein disorders. I know that this

may not be a simple question to answer. It is going to take time. It will take time to think about what has been presented here, but I would like comments from Mary as an industry representative.

DR. GUSTAFSON: Thank you, Mark, and I can't say that I can speak for all of industry right now because we are just at the end of the day. But I think this is a very good first step into a long process, and I think what has come out today are areas that need further exploration. You know, first and foremost early in the day was the issue of incentives, and there are several incentives. Under the Orphan Drug Act there is exclusivity, there are grants, there are tax incentives, but not all of those are fully utilized, and I think benchmarking other systems in other parts of the world that work very well might be one step to see what else is out there. Maybe the US system of providing incentives isn't the best one and there may be other opportunities.

You mentioned we had a presentation on the NHLBI grants, but those were small business grants, and even though these are products which would probably be low-volume products, still we feel that the best -- who would be best able to manufacture these products would really be the people who are doing it now, and they are not really small businesses. So if there could be a focus towards small

indications rather than small business, look on the product usage rather than the size of the company.

Also back to the Orphan Drug Act, orphan designation goes up to a population of 200,000. What we have talked about today are far fewer patients. So maybe even look within the Orphan Drug Act to see what flexibility there is. Maybe there could be a sliding scale. Maybe there is a little bit of room within the law between the law and the regulations that we could have a little flexibility there.

I do have to say in terms of incentives and going back to your position and the FDA, and I am glad that Jay did mention that you were flexible. But I think we all know that there are no real incentives for FDA either as a government body or as individuals working within the government to take risks that they don't have to. So I want to commend you for going forward and for looking towards being more flexible. But I think also because of the issue of change and risk that developing these flexible programs requires support top-down from your leaders within Office of Blood and CBER and FDA.

I also would say that I don't think any of our companies at all have any problems in product development, the research and development of the products in terms of wanting to take any type of shortcuts in developing a product, in their facilities, in process validation, and in

operating under good manufacturing practices or doing safety studies. The big kahuna which was mentioned yesterday are the clinical trial demands, so -- and I think, too, maybe look at it in terms of these are replacement products rather than some new, novel indication. Maybe there can be some policy decisions that could be made based on that.

I am not going to mention the word harmonize. I think what I would like to see is some optimizing on a global structure, and Dr. Epstein did mention that there are similarities in terms of the overall structure between the US and Europe is there. But the devil is always in the details, and you can have a similar structure, but by the time you start working within this regulatory framework the differences can be overwhelming and very, very burdensome. So I think, you know, that is an area, too, the Europeans are very good at putting out guidance documents early, which I think is the difference. I mean, you know, on the IVIG there is a paradigm that has been in place since 2000, but it is not really a written paradigm, you know, review paradigm. So it is helpful to industry to known what the current thinking is outside of workshops and public discussion.

There have been a lot of issues on terminology, and I think just getting the terminology down straight and making sure everyone is on the right page is important. You know,

clearly in this room today there were differences on surveillance and study. I mean, you know, hopefully most of us realize that they are very, very different, but I think that, you know, there were participants today who just kind of meshed them together. Registry and database were two others, and I think I probably could have taken down quite a few things. So getting terminology straight I think is very important.

It is getting late in the day so I probably won't go through all of these, but I think the balance between phase III and phase IV studies for these products is very, very important, and I am not talking about surveillance. I am talking about a phase IV study and making sure that it is not an endless clinical trial, and differentiating surveillance from study very, very clearly. I think probably I will end there. If any of the industry members want to say anything?

MS. HANNON: Margaret Hannon from Philadelphia. I think one of the areas of concern is that I think everyone has their own perception of the type of monitoring, GCP auditing, verification of data, cleaning of data that is required for the post-marketing application commitments. We clearly understand that when the product is still under investigational use it is the gold standard that there is 100

percent --- verification, that there is a lot of funding, resources, time and effort to get that BLA in its best shape that it can, but it appears that there is quite a bit of variability regarding what is actually required for these type of post-marketing studies. With respect to we know the product is safe, the product has proven to be efficacious, hence the product has been approved; but what is really the depth of investment that is required to do these types of studies well? Is there data that looks at the frequency of FDA inspections or audits for these studies, and what is the range regarding compliance for good clinical practices?

Because I think that really drives how quickly many of these studies get done because I think everybody, you know, has the understanding that once a product is approved your focus goes to those products that are under development. Your time, your resources, your efforts and your funding goes towards those products which are earlier in the pipeline. So in a sense these orphan products are even orphaned again because they are out there. They know they have to be done, but there is no clear sense of how much investment of those variables that we talked about with respect to business decisions are needed to do it and do it well and provide the hemophilia community and all other communities with good data.

MR. : In addition to what Mary Gustafson has told, there may be one or two or three segments of products that we can initiate to discriminate after this meeting, and those are, first of all, products that are already in the market, already registered somewhere with of course a compendium of data that we have discussed about. And I think that at this point the best thing is to have --- saying that of course the contacts should be followed on a case-by-case basis because of course having grants is probably linked to products that are under a phase of development, are not --- fully marketed anywhere. So of course grants are for development ongoing. So this is a second segment of products that could --- differently and for new products, products that are to be discovered from plasma or from anywhere else treating rare bleeding disorders. Then in such a case we are more on the prospective development plan that is naturally discussed with the authorities at a very early stage. So I think that we can in addition distinguish a couple of different segment of products with which we will cope in followup directly on a case-by-case basis which is the most important part for us at this meeting.

DR. WEINSTEIN: I just want to make sure since our time is getting very short here that, Jerry, you had some particular comments about the role that you would see in the

future for if there is something that the department might see as a way of facilitating the development of these products given what you have heard over the last couple of days. Anything new or -- I don't want to again put you on the spot, but --.

DR. HOLMBURG: Well, I think in my opening comments I mentioned the concept of the medical innovation that Secretary Thompson had put together last year, and of course all the agencies came together with their various models, of course the critical pathways that the FDA had. I think what we are really trying to do now is to try to really implement that. If you want to go to the HHS website you can see the statement on medical innovations. You can see the initiatives for each one of the agencies, and I think that is what we have to do, is we have to work together as one department with all the agencies. What that means is not just the FDA looking at the product. Of course, they have a responsibility there for the regulatory and the compliance there, but we also have other things such as, you know, with the UDC, their surveillance, you know, different aspects of that. But as we were talking yesterday with the CMS, I think Dr. Bowman did a great job of explaining some of the limitations that we are under.

However, there is -- you know, things just cannot

be linear in the way we go down the path. There has to be concurrent working the issues, and so at the same time that a product is being introduced into FDA for review and even in the early stages of clinical studies, there has to be involvement on what needs to be done on the CMS side for the reimbursement aspect of it. I would even carry that further, because we do have the CDC which is very responsible for surveillance. Now, I take a personal view of phase IV as being a real -- it is an extension of the entire approval process and so there is responsibility, and I really respect industry's concern about making sure that they have control of that information. But on the other hand, I see the benefit of the surveillance program such as the UDC down in CDC in being able to look at that subpopulation and being able to monitor for diseases, but also you have a cluster of patients there that you can check.

Now, I guess one of the things that really got me with the comments, the comment about registries talking to registries, and by the way, I -- you know, I have a thing about acronyms, and a lot of people were throwing acronyms around. I looked at my notes and I am going, okay, PMS, and I thought, oh, my.

(Laughter.)

But, you know, the idea of registries talking to

registries, I think it is not registries talking to registries unless you really have an international database commonality. But you have people talking to people, and I think that is what we have started here today, is really in the last couple of days is people talking to people. We do have mechanisms such as the international societies. We also have the World Health Organization that we can go to and work through some of these issues, and maybe that may be a step, is through the World Health Organization we do establish what are some common denominators in the approval process.

DR. WEINSTEIN: Dennis, or maybe Peter.

DR. LACHENBRUCH: Just a comment from an industry perspective. It has been stated here before as well, but the clinical endpoint that is required is a clear determinant of whether a company will go forward on a lot of these projects and how high that hurdle is. I guess the issue is if you are placing a protein that doesn't exist in somebody and you know the consequence is they are going to bleed otherwise, I am not walking away from any safety commitment or anything like that. But it seems that, you know, the efficacy, assuming the molecule is functional, is something that perhaps could be looked at. Because, you know, the longer the trial for very few patients, the harder it is for the company to justify the investment, and the earlier you can get the

product approved, the quicker the company gets a return on the investment. Which is another thing that affects the MPV models, and we have talked about grants and all those things. They are fine, but a company like ZLB Behring, we will not get a small business grant, and effectively lots of grants come with other obligations which can prove quite difficult for companies. So the grants are unrestricted; they tend to be restricted, and there are lots of issues in and around that. So there are just a couple of comments.

DR. WEINSTEIN: Dennis.

MR. : Yes. I would like turn a little bit to the policy sides of this. We talked about Congress quite a bit over the last few days and what Congress is doing, X and Y, but I think they need a seat at the table and I think we should keep them in mind going forward if we come with really a nice package of recommendations ultimately. Some of those can be on a regulatory basis, but I think there are other opportunities there. You have the User Fee Act that will be reauthorized in 2006. There could be categories under that that could even -- either it could be different types of user fees for application, greater resources going to CBER for rare disease products coming out of the User Fee Act. It could also be under appropriations for instance you could be putting together a package of report language

incentives there that would talk about registries. In other words, a complete package comprehensively of things we would like to see done, and then start working on that for next year. There is no way that is going to happen in this year's legislative cycle because they have finished their bills, but you could be working on that for next year. I think that could be a lot of opportunity there. I think we should bring them to the table, and I think industry would be happy to work on that together.

DR. WEINSTEIN: Donna.

DR. DiMICHELE: I just want to make sure that the physician/patient viewpoint gets address in the final comments, and I think I can -- I am going to speak for myself because I don't think I speak for everyone. But I think that I probably can echo the general sentiment that, you know, the physicians and the patient community that they represent are very happy that we got to this point. I think that this is something that we have been working toward I think not only nationally, but internationally for some time, and I think that the title of this part of the discussion is moving forward. I think that in no way can we not move forward. I don't believe that physician/patient community is going to let anyone move backward at this point. I think everyone needs to understand that from regulatory and from the

industry standpoint. I think we can only move forward. I think we felt very much like we are the arbitrators here among all the different factions and that, you know, we do want to continue to create a win-win situation for everyone, and we are hoping that this will be a win-win situation from the standpoint of -- from everybody's standpoint, regulators, industry, and most importantly the patients. But there is also an issue of no pain and no gain, and there will be no gain in this process without pain. Our hope is that on behalf of these patients whose standard of care I just want to remind everybody is far below that of the hemophilias that there is going to be pain in this process, and I am hoping that there will be the opportunity for all sides to compromise in terms of realizing these goals; and hopefully not years in the future, but really in an expeditious way, because we have patients out there who are hurting, and I can't have this conference end by not bringing up that point over and over again.

DR. SEITZ: After all these industry statements maybe it is also good to have a regulator statement, even if it is only a European regulator. I think first of all I have a feeling we call have a common purpose, a common problem, a common wish. We would like to see more products for rare diseases, and I think that is certainly a common thing to all

of us. What was interesting for me as a European, I have to say the openness. That the industry is talking about economic things. It is a little bit different from the European style, but I like the statement "No profit, no drug." That is a clear statement, and that is okay with me. But on the other hand I would like to say no benefit for the patient, no drug, or no safety, no drug. There are always different aspects, and I think at the end if you want to come to a win-win situation we have to take all this into account. We have to talk about money, and I am really ready to help you to make profit because this is good for the whole economy and so on, but most important is for me is that the patient will get a benefit, and how can we get that.

I think you made a very important statement yesterday. It is amazing when we have a very rare disease with only a few hundred patients in the world and we have four different agencies having different requirements. That is certainly a problem, and that is why I am here. I think that is why the FDA organized this workshop, and the question is how can we come across that. We will certainly not build up a world agency just to have rare diseases licensed. As you said, maybe we can come to a better cooperation and a better understanding of the requirements. In Europe we have a lot of experience with things like that. We have the

procedure of mutual recognition. They have a license in one member state and all the other member states have to acknowledge this license if they have not really severe objectives, and this is a difficult system because the prerequisite is mutual trust and mutual confidence, and this is not so easy to get. But I have the impression it is more and more working in Europe somehow. I think maybe in the field of such rare diseases we could come to something like mutual recognition globally. Just an idea, but maybe we should follow that.

Then maybe one comment of you I did not like so very much. You will understand that. You say that the regulators do not want to take risk. I wonder, I would really like you to know how much risk we are taking every day, but I think at least -- I can speak only for Europe. I think at least in Europe we are taking risks and we are ready to take risks to get products for rare diseases, but we do not like to gamble. There must be clear requirements, and we expect from the industry that they do what they can, not only do what is economically profitable. They really have to do what they can, but to some extent then we acknowledge, okay, this is what we can expect and nothing more.

But an important thing is if we have a mechanism like exceptional circumstances licensing with post-marketing

obligations, then we really would like to be sure that these obligations will be fulfilled, and it is not very nice to hear that in the United States you have a lot of studies licensed with the accelerated process and then the studies do not come in which were promised. This is also a point maybe the industry should think about also. This is a point of mutual confidence and of mutual trust, and if we want to come forward and really come to a win-win situation it is maybe also a point that you should take home and think about. That was my comment.

DR. WEINSTEIN: We literally have one minute before they turn off the lights here.

DR. GUSTAFSON: Could I just clarify, just because I don't want the misunderstanding. I didn't actually say that regulators don't like to take risks. I said that there is no positive incentive for a regulatory agency or the people working in it to take risks. There is a lot of disincentive. I speak to that as being five years in industry and 20 as a regulator.

DR. WEINSTEIN: Thank you. Just a comment here. First of all, we will establish a docket for all those questions that were left pending here. We would like to have people continue this dialogue, and so we will establish a site here for comments for this workshop and we will continue

discussion in that vein.

I would like again to thank again so much the efforts that the crew here at FDA, for Nisha's efforts, Jonathan's efforts, Andrew's efforts, and particularly the unsung hero of this entire meeting, Trevor Pendley*. Trevor was the fellow that brought the coffee from Starbuck's and put it on here. You did a great job. Thank you. We will meet again.

(Whereupon, the meeting was adjourned.)