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Biological Therapeutics for Rare Plasma Protein Disorders

June 13, 2005

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KEYNOTE: "---" denotes inaudible in the transcript.
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P R O C E E D I N G S

Welcome

Mark Weinstein, PhD

DR. WEINSTEIN: --- Associate Deputy Director at the Office of Blood Research and Review at CBER and I would like to welcome you to this workshop on biological therapeutics for rare plasma protein disorders. I have a few housekeeping announcements before we start this session. There first of all is no food or beverages allowed in the auditorium, and you are permitted to take off your jackets. Unfortunately I couldn't arrange for the weather here in Washington, but it is hot here. I hope that we -- we have the heat, and I hope that we shed some light on the subject of rare plasma protein disorders. We would like to make certain that pagers and cell phones are set to -- are turned off or set to vibrate. Now when you ask questions please identify yourself and activate the microphone so that we can capture your remarks on the recording. We also must be out of here by 5:30, and they turn off the lights, so we do have to make certain that we end on time. There is a cafeteria downstairs. There is also a cafeteria across the way in Natcher Hall, so you should be able to get lunch there.

We have a very full agenda today, and I urge the speakers to keep within their time limits. Our first speaker today is Dr. Jerry Holmberg. He is the Executive Secretary

of the Office of Public Health and Sciences who will present some introductory remarks. The OPHS and the FDA have worked together to make this workshop possible. Jerry.

Introduction: Office of Public Health and Science

Jerry Holmberg, PhD

DR. HOLMBERG: Thanks, Mark, and welcome to hot and humid Washington. Being an old Navy guy, I parked my car across the street at the Navy garage and walked in the hot humidity over here, so I am a little sweaty this morning, and on top of that I went to the wrong building. Somehow I was thinking of the Natcher Building, I walked in there, and they are having a seminar on chronic insomnia.

(Laughter.)

And I said hopefully this is the wrong place, so I pulled my notes out. I think that we have a lot of exciting things to discuss in the next two days, and I hope that it will not put anyone to sleep. We are very concerned about the rare protein therapies, and I am pleased that the Department of Health and Human Services along with its agency, the Food and Drug Administration, could sponsor this meeting to hear what is going on in the field of rare protein therapies.

I have really two wishes throughout this, and I was going to say something about cell phones, but Mark has already said that, but I think I will just add a little

caveat. I was at an ISBT meeting last year, and they made a suggestion that we collect a fine every time that a cell phone goes off, maybe throw it into the kitty for the -- defer the cost of the coffee. But at any rate, please honor that. I have already turned my computer to mute so that when I power it up it doesn't go through the Microsoft jingle.

I have really two hopes through this. First of all, I hope that you will realize that we are one department of the Department of Health and Human Services. We have many agencies such as the Food and Drug Administration, the CDC, and of course the reimbursement people, CMS, along with other agencies that we work with on a daily basis, and so we are very interested in what can we do to close the gap in healthcare. I wish we had a bottomless pit to draw the money from, and of course funding is always an issue. But my other hope is that you will realize that we in DC are extremely interested in plasma protein therapies and also that we are passionate about doing what is right. We are looking at evidence-based data and we want to move ahead, move science ahead very fast. Last year Secretary Thompson got the agencies together as far as what were some of the medical initiatives to move new technology forward, and as a result of that there was a document that came out with all the agencies' strategic plans. So hopefully with Secretary Levitt we will continue to move forward with that and be able

to move expeditiously on some new medical innovations.

I know we have a jam-packed next couple of days and to keep on schedule I will turn it over to Dr. Epstein.

Introduction: FDA

Dr. Jay Epstein

DR. EPSTEIN: Thank you very much, Jerry. It is my pleasure to welcome everyone on behalf of the FDA cosponsor, and my task in the next few minutes is to provide everyone with a brief overview of the meeting program. First I would like to outline our objectives, which our prime objective is to facilitate the development of products to treat patients with very rare plasma protein disorders.

(Slide.)

And pursuant to that, we will attempt to learn about the need for and the current availability of these products, to identify challenges to product development, to review current product development procedures and experience from the perspectives of regulators and sponsors, to identify opportunities to facilitate clinical trials, and to suggest new ideas for product development. So how are we going to do all of that? Well, let me just quickly run through the program.

(Slide.)

Here we are on day one, and our first session will be to look at perspectives related to defining the current

challenges to the availability of these products. We will hear about the perspective of patients and physicians; an international perspective, what is the scope of the patient population and what products are available in other countries that are not available in the US. We will discuss factors that affect industry's ability to bring new biotherapies to patients. We will look at FDA's historical experience in reviewing products for very small populations, and we will have a group discussion.

(Slide.)

The next session of the agenda will deal with defining opportunities. What are the current regulatory pathways and what incentives to development of biological products for very small populations are available to us? Again, we will look at an international point of view from the perspective of the European Medicinal Authority, EMEA. We will look at the FDA perspective on clinical trial design for very small populations. We will have a discussion of FDA's accelerated approval process, look at statistical issues pertinent to small populations, and we will look at orphan drug provisions and incentives, and again have a group discussion.

(Slide.)

We will then close the day with an overview of governmental funding support that would facilitate product

development. There is research support for the NHLBI for rare plasma protein disorders. We will look at examples of NHLBI support for the Small Business Innovative Research Support grant. We will look at opportunities that may exist in the Medicare payment program, and again have a time for discussion.

(Slide.)

Then tomorrow we will look perhaps in greater depth at some illustrative cases of product development and in particular we will look at protein C, factor XIII, antithrombin III, certain platelet disorders, and an enzyme to treat Fabry's disease.

(Slide.)

Then in the closing session tomorrow we will explore the role of post-market data collection: the experience of the FDA and EMEA with post-marketing data collection, the experience of sponsors in collecting post-marketing surveillance data through third parties, consumer group-initiated post-marketing surveillance, and opportunities for data collection through registries and through the CDC. We will then have an open discussion and then a concluding panel will attempt to frame a pathway forward.

So in closing these brief remarks, I want to give special thanks to people who made this workshop possible.

First, I want to thank Jerry Holmberg for providing both leadership and also cosponsorship support for this meeting. I know that this is an issue important to the Department of Health and Human Services as we have already stated. Then I would like to thank those individuals who helped us to develop the agenda. They formed an ad hoc scientific program committee, Donna DiMichele, Glenda Sylvester, Rainer Seitz, Mary Gustafson, and Amy Shapiro. Lastly I would like to thank the support team at FDA who worked with Mark Weinstein to make the workshop possible, and they included Nisha Jain, Jonathan Goldsmith, Andrew Chang, Trevor Penley, Dot Scott, and Jim Durham. So in the interest of time I will just turn to podium over to Mark Weinstein, who has been the chief architect of the workshop and will also chair our first session, again on current challenges. Thank you very much and welcome to all.

Current Challenges

Mark Weinstein, PhD, Session Chair

DR. WEINSTEIN: The first speaker today is Anthony Castaldo. It is really a great pleasure for me to have Anthony speak with us today. He is the President of the International Hereditary Angioedema Association, and he will discuss on a personal level the challenges the US consumer faces in obtaining products to treat very rare plasma protein disorders. His story is the ultimate reason of why we are

gathered here today.

US Consumer Perspective

Tony Castaldo, MPA

MR. CASTALDO: Thank you, Dr. Weinstein. It is really a pleasure to be here today and I think it is quite extraordinary that the patients can have a voice in such an important meeting. I will use my allotted time to share the perspectives of patients with the rare disease called hereditary angioedema, or HAE for short. A plasma-derived protein called C-1 inhibitor concentrate has been safely and effectively used to treat this disease in Western Europe and other parts of the world for well over a dozen years. Our patient community has nothing short of a desperate need for C-1 inhibitor concentrate, and we are delighted there are companies interested in licensing this product in the United States. We are also very excited that the FDA and the industry are here today to discuss ways to perhaps expedite the process for making vital plasma proteins available to treat rare diseases. Even if it is too late to revisit the current regulatory approach to licensing C-1 inhibitor concentrate, perhaps there are aspects of our experience that could influence the process for other groups of patients who are also faced with the desperate need for therapy.

Before I begin let me offer the disclaimer that insures my time with you today complies with federal law.

Although the organization that employs me is technically not a governmental entity, we are included in the Office of Government Ethics Statutes. Therefore, by law, I am precluded from representing any third party interest in this government-sponsored meeting. Accordingly, while I am the President of both the United States Hereditary Angioedema Association and the Hereditary Angioedema International, to insure strict compliance with applicable federal statutes let me state for the record I am here representing myself and my family of severely affected HAE patients.

It is always a daunting task for a patient to face such a talented group of scientists and business people who have such a keen grasp of regulatory policy, clinical trial design methodology, and the technical aspects of plasma fractionation. So to level the playing field, at least in my own mind, I came here today with the thought that even the most learned among us could benefit from listening to a range of viewpoints. I have always believed that knowing the full range of an issue’s dimensions results in better judgements because it can insure that we look before we leap.

Now these thoughts brought to mind the experience of twin brothers who actually hit the autosomal dominant jackpot because both boys inherited HAE from their mother. These bright young men did their best to live the normal life in spite of frequent HAE attacks and both were accepted to

the same medical school. In the summer before they were to begin their first year, they decided to take a quick backpacking tour of Europe and of course stop off in Italy, which indeed is the mecca for HAE research. When they got to Rome, the twins called the renowned HAE researcher and were ecstatic when the scientist not only agreed to see them, but asked if they could come over immediately and accompany him to Brussels for a talk on HAE pathophysiology.

The conference sponsors had arranged a small private propeller aircraft to take the doctor and his new friends to Brussels. Unfortunately, a few minutes after takeoff the engine’s plane caught fire and it was clear that everyone would have to parachute to safety. As the pilot tried to steer the plane over an uninhabited area, he gave his passengers some chilling news. There were only three parachutes onboard. After that bit of news and a quick calculation the scientist stood up and proclaimed, "I’m a brilliant scientist who has written hundreds of scientific papers. The world’s HAE patients and all of humanity needs me." With that, the scientist dawned some paraphernalia and jumped out of the plane. The twin brother began laughing hysterically, which did not sit well with the frantic pilot who said, "What on earth could be funny about this situation?" To which one of the twins said, "The brilliant scientist just jumped out the plane with my backpack."

HAE is a rare condition with the a genetic defect that causes a deficiency in the plasma protein C-1 inhibitor. Dysfunctional C-1 inhibitor protein permits production of basal active peptides that alter vascular permeability and cause edema. Accordingly, the disease is characterized by an episodic swelling of the extremities, face, bowel wall, and upper airway. While HAE attacks are often painful and debilitating, because edema can affect the gastrointestinal system, attacks can also be life threatening when the airway is implicated. Indeed, studies of affected --- have reported mortality rates of over 30 percent with death caused by asphyxiation due to airway closure. Tragically, Americans are still dying from HAE, and the disease recently claimed the life of a 12-year-old girl from Alabama who expired in her father’s arms from edema that totally obstructed her airway.

HAE is a catastrophic unmet medical need in the United States because there is no therapy available to treat an HAE attack once it begins. 17-alpha-alkylated anabolic steroids are useful for HAE prophylaxis in certain adults. Data from a US HAE Association reveals that many patients continue to experience periodical acute attacks notwithstanding ongoing therapy. The utility of these agents is further limited because they are not well tolerated by women and their use generally contraindicated in children,

some of whom tragically are severely affected and suffer frequent attacks. Isn't it ironic that 300-pound NFL linemen are suspended and counseled for the extreme dangers posed by relatively short course of these drugs, while our patient community is relegated to the chronic use of these toxic and highly undesirable agents.

In attempt to provide the most desperate of HAE patients with relief, the Hereditary Angeioedema Association provides technical assistance for patients wishing to purchase C-1 inhibitor concentrate under the egest of the FDA's personal importation guidelines. However, C-1 inhibitor is an expensive medicine, and no insurance company will reimburse an unlicensed therapy. Therefore, most of the patients who truly need C-1 inhibitor therapy do not have the financial wherewithal to participate. Many of those who are able to purchase the concentrate, however, soon realize there are limits on the number of times they can remortgage their homes or rely on the generosity of relatives and friends. After depleting available resources, these brave souls are now back to living with the pain, disability, and fear of death that accompanies severe HAE.

From the patient's point of view the agenda for this meeting today can be condensed into a two-part question. How much evidence is sufficient enough to support licensing of plasma protein for rare diseases, and how can regulatory

practices accommodate the multifaceted challenges posed by rare diseases that do not fit any standard mold? Our studies indicate that the regulatory framework for expedited licensure of medicines that benefit severely ill patients with unmet medical needs has been in place for over two decades. Indeed, the FDA's accelerated approval regulations were first promulgated in the 1980s by Commissioner Frank Young and subsequently codified under the Food and Drug Modernization Act of 1997.

The HAE patient community believes that our unique situation provides an excellent vehicle for exploring the issue of expedited approval. After all, HAE is a dreadful unmet medical need and there is compelling and longstanding evidence supporting the effectiveness and safety of C-1 inhibitor concentrate. For example, in Western Europe there was a sophisticated network of physician researchers who actively treat and study HAE patients. This group of world-class experts has written hundreds of papers on HAE, and every study that we have seen that discusses HAE therapy sites C-1 inhibitor concentrate as the safe and effective treatment of choice for acute HAE attacks. The viral-inactivated preparations made in Europe, and these products are the candidates for US licensure, have accumulated an extraordinary safety record over the past dozen or so years. --- filtration is yet another viral inactivation step that

will supplement patients' and physicians' confidence in this lifesaving product.

While safety surveillance data collection in Western Europe might not be as methodologically pure as some would like, there can be absolutely no doubt that any safety problems would have been detected and recorded by the formidable group of Western European HAE experts who frequently treat their patients with C-1 inhibitor concentrate. It is our opinion that the magnitude of cumulative safety and effectiveness evidence is sufficiently convincing and unequivocal, and the risks are clearly low enough to consider expedited licensure of C-1 inhibitor concentrate contingent upon successful GNP inspection with supplementary but binding agreements for intensive post-marketing surveillance and other selected studies.

The impact of regulatory decisions on human life is enormous and weighs heavy in the daily lives of many in our patient community. This is certainly the case in my family because my 20-year-old daughter suffers from an extremely severe case of HAE and is --- to androgen prophylaxis. This young woman has upwards of 20 attacks a month and a third or more involve her airway. By dent of the insane Washington, DC metropolitan real estate market, I am one of the fortunate who has been able to liquidate financial resources and purchase C-1 inhibitor concentrate. With access to an

intelligent use of therapy, this young woman has been transformed from total disability to an honor student in finance and accounting at a local university. Unfortunately, the severity of her disease is not unusual in the HAE patient community. Since Father's Day is coming up again I am reminded of the card my daughter gave me on that day last year. Her words were few, but absolutely profound and reflect the power all of you hold in your day-to-day work, and it simply says, "Dad, thanks for keeping me alive."

I will close my remarks this morning with what our patient community has dubbed the HAE clinical trial paradox. A design parameter built into a C=1 inhibitor trial stipulates that patients who arrive at the clinical trial site with a life-threatening airway edema attack will not be randomized, but instead will be given open-label C-1 inhibitor therapy. Ladies and gentlemen, I think that speaks for itself and is the perfect coda for what I have shared with you today. Thank you for giving the me the opportunity to speak with you this morning.

(Applause.)

DR. WEINSTEIN: Thank you very much, Tony. I think that was a very well-put speech and we appreciate your being here and your personal experience. We will have opportunities after this session as Jay has mentioned here for panel discussion with all the speakers in this session

and we will be able to discuss in some detail the proposals that have been made here, and in the rest of this meeting in fact on the suggestions that you have made for your clinical trial approach.

International Perspective

Flora Peyvandi, MD

DR. WEINSTEIN: Our next speaker is Dr. Flora Peyvandi. She is the Chair of the Working Group on Rare Blood Disorders of the Factor VIII/IX Subcommittee of the International Society of Thrombosis Hemostasis. She will give a view of the international perspective on the need for these products and a review of some of the products that are currently available in the United States and elsewhere to treat rare plasma protein disorders. Thank you, Flora, for coming all the way from Italy to attend this meeting.

DR. PEYVANDI: Good morning, everybody, and thank you for inviting me and giving me this opportunity to talk about what is already available for people who are affected with rare protein disorder and what is the situation of these patients in the world and what we have available to treat them. Just to get the section why we need a working group under the subcommittee of the ISTH, I think we need to go a little bit about the background of rare protein disorder, what they are and how these people are usually treated and what is the most clinical manifestation in these patients.

(Slide.)

These disorders are usually inherited as autosomal recessive disorder, and the numbers in the general population is approximately one case in 500,000 for factor VII deficiency for example, and for the rarest one like factor XIII or hyperprotein anemia is one case in every two- or three-million of the general population. These numbers are significantly increasing in some areas of the developing countries because of higher frequency of consanguineous marriages, and the numbers of the patients sometimes is touching like hemophilia B populations in these countries then you can address then they are requiring really a more demand for the diagnosis and treatment.

(Slide.)

These type of diseases as in orphan diseases until very recently there were really neglected by every organization, pharmaceutical companies, and this type of patient, they were absolutely orphans without any type of facility for the diagnosis and treatment.

(Slide.)

So what is the clinical manifestation in these people? We tried to make an international registry to collect more data available in the world because since 1996 there were only a few reports reported by each single

researcher or groups around the world, and it was very hard to understand, which is exactly the clinical situation of these patients. So what is the best treatment for these people? What is the best type of prophylaxis? The first is we thought that maybe put together the information and try to find some type of guideline, at least for the starting point. These data that I am reporting here is coming from different patients around the world, with more than 200 families, around 700 to 800 patients. Totally we can say that these types of patients, they are bleeding less severely than hemophilia A and B and the life and limb threatening symptoms are usually less frequent. The type of bleeding in this patient could be very various, from mild to moderate, and could sometimes also be very severe.

(Slide.)

Here is a conclusion of what is the difference between hemophilic patients and compared to the rare bleeding disorder. The grey bars, they are showing the hemophilia patient. You can see the joint and muscle --- are much more frequent. For rare bleeding disorder, the mucosal type of bleeding are really important, and especially in the women. More than 50 percent of the women who are affected with rare bleeding disorder are chronically anemic and they have to be treated with the chronic type of treatment for all their life.

(Slide.)

This slide is a complicated slide but it is a result of four or five slides together. I tried to compare each single disorder compared to the hemophilia, which you can see on the left side if reported. On the left side I have got all the clinical information on 100 patients of severe hemophilia A and the red color in the middle is showing the personal prevalence of each single severe bleeding symptom, and the blue one the mucosal type of the bleeding. On the right side, the group of each single deficiency like --- anemia, factor II deficiency, factor IV, V, VII, X, XI and XIII was compared and the intensity of bleeding was compared with intensity of the color. As you can see, factor X is one of the most severe bleeding symptoms, and I remember when I was in one of the Middle East countries more than 89 percent of these patients, they were HCV-positive just last year. We are not talking about ‘80s, and most of them also were HIV-positive. That means these types of patients, they are requiring a huge number of treatments, and since there is no concentrate available in this area, they are still treated with plasma and not --- inactivated type of plasma. Then factor XIII deficiency is an important disease because a little amount of factor XII is enough and it is sufficient to prevent the bleeding symptom, the severe type of CNS bleeding and miscarriages in the

women. Just 25 percent is enough. So the prophylaxis is a very important issue in this group of patients. Factor V and factor V and VIII deficiency are less severe, but once you have a patient with this type of disease it is hard to treat them because the only available product is plasma, and we have no factor V concentrate available. Factor II deficiency and hyper-fibrinogen anemia, they are the patients sometimes that are requiring prophylaxis treatment because of joint and muscle bleeding.

(Slide.)

Once we make the diagnosis it is starting the most severe section of the rare bleeding disorder, how we are going to treat them. So there are few long-term prospective studies only available on the large cohort of patients, and that makes it very difficult to give us enough information about how to treat and how to manage these patients. The coagulation factor support may require the prescription in most of the countries of unlicensed treatment products which are not readily available. The purified factor concentrates are not as readily available as it is for hemophilia, and how we can see now that we are at the third generation of the recombinant product for hemophilia for factor VII, but still we have really no suitable treatment for these type of diseases.

(Slide.)

Mainly the treatment of rare bleeding disorder is focused by replacement therapy and non-transfusional treatment.

(Slide.)

I am just talking about the replacement therapy today, and all of us, we know the backbone of the treatment is fresh-frozen plasma which contains all coagulation factors, is inexpensive, and is widely available in the world. But of course it is very important to find the virus-inactivated FFP, which is really a very small amount of the available product in the world.

(Slide.)

A few single-factor plasma-derived fibrinogen factor VII, factor XII and factor XIII concentrates are licensed in some European countries and hardly distributed uniformly in all Europe, and very few in the States. The prothrombin and factor X deficiencies are often treated with prothrombin complex concentrates, and that sometimes makes a problem when you have a patient with thrombophelia history because that contains an unnecessary amount of vitamin K factor over the actually deficient ones. There was really little progress in the treatment of rare bleeding disorders because we have only one recombinant product, which is factor VII-a recently licensed for factor VII deficiency in Europe, but still not licensed in the States for factor VII

deficiency.

(Slide.)

Factor V and V and VII deficiency could be only treated with fresh-frozen plasma.

(Slide.)

Here you can see the factor concentrates available reported by Dr. Casper and the World Federation of Hemophilia. As you can see, there are different companies producing, at least it is reported, the different concentrates. But to my understanding and to my experience, in some of the countries the distribution is not really as reported in the literature. So fibrinogen is completely missing in Italy and once I have a patient with severe bleeding I have to order it by international community, and it is taking me like two weeks to have the product.

(Slide.)

This is the prothrombin complex concentrates, and still you can see there are different companies producing this product.

(Slide.)

But since I had the feeling we need to establish a better distribution in the world of these products, I sent a questionnaire to all the companies asking which product they are still producing which could be useful in rare bleeding disorder, is there any type of variation in the production of

the manufacturing, are they using any type of plasma-derived product, how is the situation with the virus inactivation, which method they are using, there was any type of improvement of the virus inactivation methods, which type of rare bleeding disorder is the focus of their products, and in which region of the world they are usually distributed.

(Slide.)

The last question was answered really by very few companies, and this was the result that I obtained. So the questionnaire has been sent to 23 pharmaceutical companies, and 43 percent, they have answered to my question. Four of them, they had no more production, but we will see how is the result. So these are the companies that answered to the question, four persons. American Red Cross is no longer producing this product. Mostly, 70 percent, they have no change and there is no variation, and as you can see they are also reporting the data on factor VIII or factor IX. I was surprised they didn’t even mention for rare bleeding disorders other types of the disorder, and only LFB was reporting the production of a new product, the fibrinogen, and no other product is still in the production of the new manufacturing.

(Slide.)

So only one new product for fibrinogen deficiency emerged from the questionnaire. The trend of pharmaceutical

manufacture research is principally focused on new products to treat the hemophilic patient.

(Slide.)

I see in literature very recently where the ZymoGenetics Company is producing a new recombinant product of factor XIII. This product is a recombinant factor XIII A2 homodiner produced by yeast and was used in 50 healthy adult volunteers. The result was good with the product was well tolerated with no serious adverse events or dose-related toxicity. However, I think we need to see the result of this product in the patient affected by factor XIII deficiency.

(Slide.)

What about the guidelines? In the literature we can find two guidelines, one with Mannucci and myself under recessively inherited coagulation disorders published in Blood in 2004. The other one from Dr. Bolton-Maggs reported in Haemophilia in 2004, and still I think both of these two results, they couldn't cover lots of information.

(Slide.)

Which could not be covered if we don't put all our forces together making an international registry putting all information together and trying to constantly follow drug production, cost of the product, the distribution of the product in the world. We have to try to make a guideline treatment for difficult situation on demand, prophylaxis,

neonate, children, the women during the pregnancy, for the women with a problem of minuartia, and long treatment. We need to know if the patient with heterozygosity and with the mild or moderate level of different factor needs to be treated, and we also need to know how safe is the prothrombin complex. So all this information needs to be done with the different groups, and I think the only working group under --- of the clinical people coming from different areas of the world and the experts who for years and years have to do for these patients could make together the force and make the unique information which could be used for the clinician and also for the patient. Thank you for your information and attention.

(Applause.)

DR. WEINSTEIN: I think we could have just perhaps a few questions if someone has some questions that they would like to ask at this point, or we could wait until the end of the panel discussion at the end of this session. Okay. If not, we will just go on.

Physician Perspective

Amy Shapiro, MD

DR. WEINSTEIN: Our next speaker is Dr. Amy Shapiro. She is the Medical Director of the Indiana Hemophilia and Thrombosis Center and she will discuss the challenges faced by physicians in attempting to treat

patients with rare plasma protein disorders. She will present a case study of her struggles to develop a biological therapeutic to treat a rare disease. I should also mention that Amy's efforts to make the plight of under-served patients visible was one of the major driving forces that lead to the development of this workshop. Amy.

DR. SHAPIRO: Thank you, Dr. Weinstein, and thank you for inviting me here today. I promised Mark that I would keep this to 20 minutes, so I am glad to see that we are ahead of time, and I might have an extra minute or two. But I am also glad that Flora did such a wonderful job presenting this information, so some of what I have is redundant and I will be able to flip over quickly.

(Slide.)

So I was going to present today rare bleeding disorders and the physician's perspective on therapeutic needs, provide you some background information and some data on rare deficiencies, which Flora has done so we can go over that quickly, present to you a case in point. I brought the handouts with me. They were at the front desk. I hope you all have them. Attached to the back of them are two letters from two families that I take care of that discuss their care, and some proposals for moving forward.

(Slide.)

In the United States, the definition of a rare

disorder is a disease or condition that affects fewer than 200,000 Americans.

(Slide.)

As Dr. Peyvandi very well pointed out, factor VII deficiency fits in that category very well, affecting about one in 500,000 population. There are two registries that include these patients. She has discussed some of this information.

(Slide.)

There are other factor deficiencies, bleeding disorder for the most part, that also fit this definition. Some of these have specific replacement products, although they may not be licensed in the United States. However, these products may yet still not be ideal, even though they exist, because they may be plasma derived. But a recombinant replacement product may never be developed for these diseases due to the rarity, the patient pool for which they would be utilized, and the cost of production.

The real issue are other deficiencies that are so rare to preclude development of a specific replacement product, including, as Dr. Peyvandi mentioned, factor V deficiency, X, II, plasminogin, alpha-2 antiplasmin.

(Slide.)

The issues are in treatment the ability to obtain an efficacious product and the knowledge of an appropriate

replacement strategy for these patients, and because there are so few patients and because we have not very good products, it is difficult as a treating physician to garner this information. There are clearly barriers in the development of adequate replacement products: the cost of research, the cost of clinical trials which is immense, a limited market in which to utilize them, and the regulatory burden on the manufacturer and the investigator. In terms of development of clinical trials, one of the problems is the adequate number of patients, and the issue is we like to get compliant patients into clinical trials so that we know we can get the required data points. But the problem is that not all patients with rare deficiencies are as compliant as we would like them to be to participate in a clinical trial, but these individuals are still deserving adequate care.

(Slide.)

Well, reimbursement then becomes an issue for these patients. It is very difficult or you are unable to obtain insurance coverage for therapy if this product is imported for personal use or is used off label. Importation and off-label use are really not adequate long-term solutions for treatment of these patients, and given the high price of medications in general this issue is becoming increasingly important as Medicare, Medicaid, and hospital budgets are increasingly constrained.

(Slide.)

So patients with rare deficiencies have very limited options for care. Their standard of care is often far lower than that of hemophilia, and they suffer increased morbidity and mortality.

(Slide.)

So where are you with a rare disorder? And this is sort of an algorithm I put together as I was struggling through trying to find some products for my patients. You could be in the category of having a product licensed in the United States but not for this indication. For example, that could be factor VII deficiency and the use of recombinant VII-a. If you are lucky, the product may be available in the United States. If you are not so lucky, the product may not be available in the United States.

Then the question, which I didn’t know until I bumped into it, was whether the manufacturer’s BLA is up to date with the FDA. You could be in the category of not having a product licensed in the United States for use either on or off label, but maybe that product is licensed outside of the United States for that particular indication. For example, that could be protein C concentrate. Or perhaps the product is licensed outside of the United States but not for this indication. Again, an off-label use. Then you could be in the category of no product in or outside the United States

for use either on or off label. That is not a good category.

(Slide.)

So here is where you have a problem. The biggest problem for treating physicians is the product is not available in the United States and the manufacturer's BLA is not up to date, the product is licensed outside of the United States but not for this indication, which makes importation more difficult, and there is no product available either in the US or outside.

(Slide.)

So I would like to talk just a little bit about a disease called ligneous conjunctivitis, which started my quest on rare diseases. I thought it was interesting when I first got the patient referred to me, and now it has become more of a heart-wrenching event. This is a rare disease that is characterized by formation of thick membranes of the palpebra surfaces which progress to thick nodular masses that replace the normal mucosa. It may be precipitated by an infection or some incidental injury. The pseudomembranes are lesions that may be observed in the mucosa of other areas, including the mouth, tongue, nasopharynx, tracheobronchial tree, female genital tract. They may lead to loss of sight, hearing, teeth, sterility, hydrocephalus, dysmenorrhea, chronic sinus or pulmonary disease and death, and it has been demonstrated to be due to a deficiency of a plasma clotting

factor, plasminogen.

(Slide.)

Plasminogen deficiency manifestations, as I eluded to, do not just include ligneous conjunctivitis, but also oral lesions which can be termed ligneous gingivitis; lesions of the female genitourinary tract, or ligneous cervicitis or vaginitis; hydrocephalus; and ear, sinus, and tracheobronchial tree abnormalities, and if the obstruct the tracheobronchia tree may cause death.

(Slide.)

This is a picture of an infant who is reported in the New England Journal of Medicine in 1998 with ligneous conjunctivitis, and you can see that his eyes are completed occluded by these woody membranes, which cause corneal abrasion and scarring and blindness. This infant was treated with a plasminogen concentrate which is no longer available.

(Slide.)

As I began to explore what treatment options were available or had been used and reported in the literature for the treatment of this disease, I developed a list of therapies. There are some therapies that have been used just topically, and there are others that have been used systemically. I have stared -- I have put a personal efficacy rating on some of these. The ones that are unstared are not even considered to be of even minor efficaciousness.

The ones that are stared have some efficaciousness, but for example excision may be important to do because of the occlusion of the eye, but it leads to a recurrent cycle of regrowth of membranes due to the surgery and removal of the membrane itself. So it is not a good long-term solution.

The best products that have been utilized include the use of plasminogen, either topically for example as an eye drop as a solution, or systemically.

(Slide.)

This is that same baby after treatment with systemic plasminogen concentrate. You can see there is a huge difference with regression of the membranes.

(Slide.)

So I had patient referred to me in 2002 by an ophthalmologist who had ligneous conjunctivitis when he read some reports that this was associated with plasminogen deficiency and obtained some plasminogen levels on this individual and documented that that was indeed his problem. The review of the literature that I did at that point revealed that a drug called Eminase was efficacious for local therapy. This is a drug that is used as a fibrinolytic agent systemically given intravenously. However, because the market in the United States for fibrinolytic agents has been taken over essentially by recombinant proteins, this drug was no longer marketed in the United States for that specific

indication. However, it was still utilized in Europe and marketed there. It contains plasminogen and streptokinase.

I contacted the manufacturer of Eminase, who initially seemed willing to provide the drug to the patient for free. I contacted the FDA to do it right because I didn't want to do anything behind anyone's back and break any laws, and I was asked to file an IND. I reviewed with the FDA in a very nice conversation the work that was required to accomplish this from both the investigator side and the manufacturer side. What I found out in terms of the IND was there was tremendous amount of time required from the investigator to put this together, and the manufacturer must have an updated biologics license application at the FDA. Unfortunately because Eminase no longer had a market in the United States, although it was technically licensed, their BLA was not up to date.

So in the end, as Mother Teresa said, no money, no mission. Everything has a cost. There were no funds available to reimburse the time to do this, and the manufacturer decided that financially it was not feasible for them to update their BLA with the FDA when the potential market for the drug did not exist in the US and then what they would be doing is supplying the drug for free as well. So it was a total financial loss for the company from that standpoint.

(Slide.)

So then I went to look for how else can I possibly get this drug. I called Canada and found out it was not available there either, so going over the border wasn't helpful. We could write a prescription and have either myself or the patient import a personal supply of the drug, and as we heard this morning the company didn't want to donate the drug due to the cost and the fear of legal repercussions if they donated, and the patient unfortunately didn't have enough money for travel. Even if we got the travel donated by some charitable organization, they couldn't pay for the drug once they got, for example, to Germany to get a prescription filled.

(Slide.)

In the end, what I realized is that really plasminogen deficiency is a systemic disease, and I now have more than one patient. I have the patient who has ligneous conjunctivitis who also has sinus disease; I have one patient with ligneous cervicitis, infertility, sinus and ear disease, and a history of ligneous conjunctivitis which she presently does not have now; and I have two patients with ligneous gingivitis, one of who has associated cervicitis, hearing loss, and sinus disease.

The optimal treatment for these patients is either some medication with demonstrated efficacy that can be used

locally in a variety of sites -- and it is hard to think about using Eminase as a douche or in other areas, in your ear when it is the middle ear that is affected -- or a systemic medication, a plasminogen-replacement product.

(Slide.)

So I went in search of plasminogen. There was one report in the literature in the New England Journal of Medicine using a plasminogen concentrate, but this company no longer manufactures that product and was not willing to remanufacture that product. Interestingly since plasminogen is part of Eminase, the plasminogen that is part of it is plasma-derived and is of clinical grade because it is used both intravenously and topically. But I could not find out the plasminogen supplier to the manufacturer to obtain this one component. Plasmin is presently in clinical trials. It is manufactured from plasminogen. This is a plasma-derived product, but step at which plasminogen is available is not again at clinical grade. Plasmin itself is not efficacious for the treatment of this disease due to inactivation locally very rapidly in the tears by antiplasmins, and there was a concern from the company that was developing this product about the use of an investigational product for an off-investigational use in terms of how it might potentially derail their entire research program.

So then there were some reports about making your

own plasminogen, and on some nights of desperation I thought about this. There are issues about the costs of doing this and how to get financially reimbursed for it. We didn't think that that was possible, but even if you put that aside there were the issues of the consistency of the product that we could produce on our own and the viral inactivation, which would not be available. Then there were legal and regulatory concerns. So although it is published in the literature that people are doing this, there are concerns about making products such as this and utilizing it for individual patients.

(Slide.)

So how do we move forward for these patients? Well, clearly it seems to me that we need to form a coalition of agencies all with mutual interests in these populations. This could include NHF, ISTH, the World Federation, NORD, and other interested agencies.

(Slide.)

We need to work with the FDA and industry to develop mechanisms to allow improved access to these therapies. Some of those could include obtaining another licensed indication for an already-licensed drug -- for example, NovlSeven for factor VII deficiency; obtain a product that is licensed in another country for use in the United States for which we have no viral-inactivated

alternative; or produce a product that does not yet exist -- for example, plasminogen or factor V concentrate.

(Slide.)

We would like to work with the FDA and industry to develop mechanisms to allow improved access to therapies. Is it possible for the FDA and EMEA to harmonize its processes for these rare patients only so that we can pool our data and make things available across borders? Can we explore alternative mechanisms of drug importation with the FDA that may allow payment?

(Slide.)

Due to rarity of these disorders and lack of universal adequate available therapy, trials such as we understand them and utilize them in hemophilia may not be feasible in these patient populations.

(Slide.)

There are different kinds of trials that can be performed: pharmaceutical sponsored trials, investigator-initiated IND processes. These processes may be difficult. Can we streamline them? Is investigator support available for the time required to do this? The use of registry data to support license indication is difficult. It is not always prospective data. It is not always controlled, but maybe we should consider this for very rare diseases, and we need to encourage registries through independent organizations so

that they are as unbiased as possible.

(Slide.)

As will be discussed later today, obtaining orphan drug status based upon a therapeutic indication for a rare disorder provides incentives for drug companies, and I have listed these just from my own knowledge so that when I call these companies begging for something and trying to get some help I try to remind them of this in case they are applying for anything else to keep that in mind, and that very small populations in the past have been used to get licensure for some rare products, including Ceredase and peg-ADA.

(Slide.)

Off-label use of currently licensed products, the incentive to the manufacturer may be small business innovative research grants, may be a six-month patent extension, which can translate into a lot of dollars if a drug is invested for example in a pediatric population even if the treatment of the rare disorder represents a non-profitable group. We need to encourage synchronization of European and United States regulatory agencies for these disorders to prevent repetitive work and increased financial burden on the manufacturer. Every time we have to repeat these studies it costs more.

(Slide.)

There are aims that we have to keep in mind when we

do these trials. We want safety data. We want determination of efficacy. We want to know at least the risk-benefit ratio, especially when we explain these to patients, and we need some dosing guidelines. We need to collect adequate data to obtain approval through regulatory agencies whenever possible. We need to do our best.

(Slide.)

We need to base these studies on the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice. We need consistent and verifiable data, and we need a commitment for followup from the investigators and the patients.

(Slide.)

In summary, rare disorders have limited therapeutic options. Patients suffering from these diseases need access to adequate therapy whenever it is available. Clinicians require technical assistance to deal with manufacturers and regulatory agencies to assure that their patients have access to these therapies, and we need multinational studies to obtain adequate patient numbers.

(Slide.)

One concept is the development of a multi-organizational clearinghouse or resource center for the purpose of assisting clinicians, searching for treatment options, protocol development, interfacing with regulatory

agencies, and to find companies that can assist in obtaining orphan drug status throughout the world. We need to also consider the development and maintenance of listings of interested private and governmental agencies; manufacturers with potentially effective therapies either licensed or in clinical trials, because it is very difficult to find manufacturers with products in clinical trials that could be potentially efficacious for this population; and those companies who may have an interest in assuming a product portfolio for limited indications. Thank you.

(Applause.)

DR. WEINSTEIN: Thank you very much, Amy. We appreciate those comments, and again we have a few moments for questions if you would like to ask Amy a few things. Okay. I again have been reminded to remind you that we do not allow food in the auditorium. Please do not eat or drink in the auditorium.

Factors Impacting Industry's Ability to Bring New Biotherapies to Patients

Paul Walton, PhD

DR. WEINSTEIN: Our speaker is Dr. Paul Walton. He is the Senior Vice President of Business Development at ZLB Behring, and he will talk to us about factors impacting industry's ability to bring new biotherapies to patients. I think this is really a critically important topic, because by

understanding the costs that are involved in a sponsor's decision to develop a product for a rare disorder we may be able to identify incentives and opportunities to make their decision to go forward more attractive. So, Paul.

DR. WALTON: I would like to thank the program organizers for inviting -- particularly Mark Weinstein and Mary Gustafson, for inviting me to present today. What I am going to give is a perspective on how for-profit manufacturers approach investments to bring new therapies to market with some concluding comments that I think are relevant for the discussion today on rare disorders.

(Slide.)

So in my outline I would like to walk you through some of the background that impacts decision-making in industry, some background on the value and economics of plasma biotherapeutics. I want to show you one of the mechanisms we use, and it is one of the mechanisms. I make the point this is not the only approach the for-profit industry takes, but this is a very important approach, which is using investment analysis techniques and decision rules to bring new therapies to market. Then to conclude I want to go through some of the factors that impact our decision to proceed or not, and in fact if I have time I have a couple of simulated analysis to show you how these analyses are done and come to a final decision.

(Slide.)

To begin with, I thought it would be worthwhile to make the point that all organizations, whether they are for-profit enterprises like my company or not, deliver value in some form. They fill a need. If the organization delivers value and adds value, then it continues to exist and thrive. If something interrupts that value creation, we end up with change. I make this point because in the plasma protein therapeutic area there has been a lot of change in the last five or ten years precisely due to this factor that owners or stakeholders perceived value not being delivered and changes have taken place. You could probably write several case studies on the plasma therapeutics business in this context.

(Slide.)

I would also like to just simply review some of those factors that we have to consider in running a for-profit enterprise. The business internally obviously under leadership determine strategy, planning, and business processes. Externally though we have to consider our supply chain and our product chain and raw materials for our product, principally plasma. We have to consider safety and supply issues, costs. On the production side for products and services we look at our markets, and quite often consumers are several steps removed from us. The end user often is further down the distribution chain, being a

physician or patient who receives the product, so we need to respond to their needs and come up with appropriate products and services.

In addition to this, we have a lot of inputs. Certainly government regulations and polices, economic conditions, particularly for those companies that operate in a number of arenas. We operate in Europe, Asia, the United States, Latin America, and almost all economies, so we have to consider each of those jurisdictions separately. We have to consider society and the community concerns that impact our business. For most of us we have a parent corporation, and they set priorities. The majority of those priorities fit with our strategic goals, some of which are financial. It is important to also consider we have a lot of resource provision considerations. There are organizations that provide for us technology people, money. For publicly-listed companies with shareholders they provide capital. The majority of companies in this sector are publicly listed. The shareholders in return expect dividends and equity in the organization. Finally, we have to consider our competitors, who look to competing with us for resources and also into the marketplace. So this just sort of simply gives the bird's-eye view of the number of factors that we must consider in running an organization.

(Slide.)

Put simply, I see our business as basically a creator of value, a machine that takes as an input shareholders' money and plasma and develops products. We have a responsibility to patients who require these therapies and to those shareholders who provide the money to drive the engine. We run through clinical development, capital investment, launch, production, et cetera, and if it works well we produce therapies for patients who need it and we produce dividends for shareholders. But I want to point out, and I think this is fairly obvious, there is a significant risk in this business which would shut down this machinery.

(Slide.)

I will focus on shareholders for a minute. It is pretty obvious if they are not satisfied with their return on investments they have options such as investing in the competition or other sectors or other geographies. So we have to consider their appetite for risk, which is proportional to the return that they expect. We have to understand what our investors are looking for when investing in our organization. They generally have two questions: What they will be paid for the use of their money and when they will be paid. We consider in our thinking the rate of return on investment. In other words, what our investors are looking at in return for the risks in return for the use of their money, and well-managed enterprises should know what

their shareholders want.

(Slide.)

Before I go into some of the mechanisms to look at those things, I wanted to put this slide up. This is a slide that I think has been shown quite a lot in the plasma therapeutics area to compare the cost economics of plasma therapeutics versus big pharmaceutical companies. What I have done is here is designated the cost base roughly for the plasma industry, typical plasma products producer, to a large pharma small molecule producer; and I think the point I wanted to make is the plasma industry has one consideration, the cost of plasma, which drives up our raw material costs. The other issue is that the majority of our resources for development of new therapies come out of R&D and marketing, and typically in our business that is about 15 to 20 percent of our costs versus about 45 to 50 percent of the cost base for classic pharmaceuticals.

(Slide.)

So when we are faced with decisions that involve significant capital and other investments, long time lines prior to launch, complexity and risk such as the development of a new biotherapy, we have to use a technique to make decisions; and we employ typically investment analysis techniques. There are a number of these I have listed here. They are essentially financial tools. In our organization we

look at cash flow, we look at value that is generated. Basically we follow this decision-making tree. We start with a proposal. We try to build as best the assumptions for that project. We run through our investment evaluation techniques, go through our decision-making rules, look at advantages and disadvantages. We look at qualitative factors, and I will mention some more about these later. We look at investment alternatives and we make a decision evaluation on whether to proceed with the project, and we continually do this. Once a project starts, we go back and reassess whether the initial assumptions were correct.

(Slide.)

The method of choice we typically use is net present value, and this is a calculation of the present value of any investment project, but in this case launch of a new biotherapeutic based on its expected future cash flow generated by the project, but taking into account time, the initial investment, and risks. The advantages of this method for us is that it helps us capture the concept of time over very long time frames, usually a decade or more. We can establish cutoff rate. In other words, a level at which we expect the project to return respective to risks. It is based on cash flow, not profit, so it accounts for capital investment as well as revenue and expenses, which financially is a much more transparent approach. It is well understood

and accepted. It is usually combined with net cash flow in or out of the project, and, as I said, it accounts for risks.

(Slide.)

This shows the methodology, but fortunately we don’t have to memorize this. It is one of the pull-down menus in Excel accounting formulas, but it is important to actually understand what it s made of. The R value is annual cash flow for each year that we run the model. Typically you run these over decades. So it shows cash flow in or out of the case for a number of years. The C indicates initial cash outlay, and then we have this factor called discount rate which is the opportunity cost of capital. Again, this is a factor that our shareholders are most interested in. It is the required rate of return or the cutoff rate. In other words, the project has to return this percentage to shareholders to be acceptable. The decision rule is quite simply you would accept a project if the net present value is greater than zero or you would reject it if it were zero or negative. In fact, you often in looking at a number of different projects, so you are doing a comparison between other projects and assessing present value in cash flows.

(Slide.)

There are a number of factors that influence NPV, the NPV investment model or in fact any of these investment models. To begin with capital investment, does this project

involve for us to upgrade an existing plant, or in fact build a new plant. This is a fairly significant component in our decision making. Clinical trials, the size, the number of patients, the cost per patient, the jurisdiction, the cost of putting together CMC materials, other regulatory costs. The manufacturing cost of goods. This depends on the yields. If you have a very, very low yielding product, you might find the manufacturing cost of goods to extraordinarily high. It depends on the impact on the rest of the process. Often if you have to remove a new product from plasma it does have an impact on the upstream or downstream impact on the other products that you are pulling from plasma. The commercial expenses, whether you need to invest in sales and marketing, medical marketing, registrations, and post-marketing trials. These are all factors that in fact remove cash from the model and have to be considered.

Now a number of factors impact cash going into the model: The market launch date, the number of patients, the time of peak sales, in-market pricing and reimbursement. The territorial jurisdiction, there are differences in these different markets that impact the costs. Competition, if there are alternative treatments being developed or on the horizon. If you are in a horse race against a product that may in fact increase your risks that has to in fact be taken into account in the model; whether there are replacement

therapies, whether you have me-too products that other companies may have on the market or plan to launch.

(Slide.)

To demonstrate how this works in our hands I would like to actually show you some simulations of investment cases, and I have put together -- these are not real cases, but the numbers are in fact the order of magnitude that we would have in a real-case plasma therapeutic. So I have put together a base case that would be fundable, and I put together three other cases. One where we would assume that the original clinical trial assumptions were incorrect and we discovered halfway through the process that clinical trial costs were greater due to either added costs or delay in launch. A second case, a rare disease where we have a small number of patients. The third case would be where we would have all other things being equal, but where we would have a very high risk of failure during the clinical development due to some very difficult-to-obtain clinical end point.

(Slide.)

If we just look at our base case for comparison, what I have done is put together a case here where we are considering registration of a product in both Europe and the United States from today launching in 2010/2011, which I think is actually an optimistic time frame. We would assume this is a product that replaces one on the market, so you

would have some advantages in time. You would obtain peak sales in four years with 500,000 treatments per year. So 10,000 patients at one treatment per week. This would certainly be classified as an orphan drug, but it is typical of some of the plasma products that we manufacture. Development costs are quite modest, $15-million for preclinical CMSs, clinicals, regulatory, et cetera. Again, that is quite low by comparison to what the pharmaceutical industry faces, but it could be typical for a product where we already have some sunk investment and skills. A capital investment of $3-million just to maybe upgrade compliance in the plant.

(Slide.)

So you can see this is actually not a significant amount of investment. If we run the investment analysis at a 10-percent discount rate, which is more or less about where we run these analyses, we see that we have a net present value of $27-million over a period in time. We would give this a green light. You can see on the right side here showing cash flows, initially negative for a number of years until launch, and then a building in cash flow for the company.

(Slide.)

If we look at exactly the same case but we vary one aspect, we got the original assumptions wrong, that the

launch was delayed by three years, that the development costs blew out to $25-million. We lost time, so therefore the in-market pricing was reduced due to increased competition, and the investment risk is now higher, so we have increased our discount rate to 14 percent.

(Slide.)

This situation gives us a negative net present value. You can see a number of years of negative cash flows before we have the same cash flow from the marketplace. Business would probably decide not to proceed on this basis.

(Slide.)

If we look again at the same situation, keeping everything fixed with the exception that now we have reduced from 500,000 treatments down to 30,000 treatments per year, which would equate to 600 patients at one treatment per week. This would also be similar to if you had a situation where you had a very poorly competitive product.

(Slide.)

Keeping everything the same, what we see here is a highly negative net present value. The cash flow is at the front. The front end is the same. The scale is really impacted by cash flows once the product is launched. We have a very difficult situation. There are few ways that one could remedy this; by looking at the development costs and trying to reduce those to make this a positive decision.

Another approach would be a massive increase in the cost of the product, and I have indicated here in this particular model a 15-fold increase in price would be required to bring this to a break-even point.

(Slide.)

If we have difficult endpoint, in other words if our R&D director tells us that we have a much higher risk of failing through the clinical trials, and again keeping everything the same, we can do two things. We can either invest at the front end in decreasing the risk of the failure with the clinical trial. Alternatively, we can add more risk by increasing the discount factor.

(Slide.)

What I have done here is run the same model keeping everything the same, but using investment analysis at a high rate. So I have used a 20-percent discount rate. You can see whilst the cash flow is kept the same as the base case, we have a negative net present value, and the business decision would be most probably not to proceed with this project.

(Slide.)

As I said, this is only a tool. Qualitative factors must also be considered. These are relative factors that can’t be expressed in financial terms, and we do consider these. Moral values of the company enter into the

decision. There may be other benefits that are not reflected in the financial model. There may be urgency or persuasion criteria where the company decides on benevolence.

(Slide.)

My conclusions are these. These techniques are used by management when deciding to bring biotherapeutics to patients. Some recent examples in where rare diseases have been successfully subjected to this analysis include alpha-1 proteinase inhibitor, C1 esterase inhibitor. An example of where a decision not to proceed -- and this is not just in my company. Others have made the same decision -- is the aerosol delivery of alpha-1 proteinase inhibitor. There have been projects started and then put on the hold on the basis of failing due to this type of analysis. The technique is impacted by development costs, the size of clinical trials, risk, and patient numbers.

(Slide.)

In the case of rare diseases, the major factors that impact the decision rule are the number of patients that require the treatment, in-market issues such as expected reimbursement and product pricing and competition between therapies, the cost of manufacturing. We are often technically constrained by the manufacturing of other plasma biotherapies, and putting the manufacture of those products at risk is not an option. The cost of CMC preparation, the

cost of clinical trials and the practicality of completing these, the time taken to launch and then reach peak distribution, and anticipated life cycle of the therapy relative to other technologies that may cause redundancy. These are all factors that would impact a decision.

(Slide.)

As I said, non-financial factors are also considered, but in the end I want to make the point that companies do require capital from shareholders to survive. This type of analysis secures trust from our shareholders and for us secures a provision of capital to continue to be able to develop and manufacture therapies. Thank you.

(Applause.)

DR. WEINSTEIN: Thank you very much, Paul. Again, we might have an opportunity. Donna DiMichele would like to ask a question, Paul, if you would like to come up here for --

DR. DiMICHELE: No problem. You could probably address it from there I'm sure.

DR. WEINSTEIN: Well, again, we will have time for further discussion and panel.

DR. DiMICHELE: I just wanted to -- Donna DiMichele from New York. I just wanted to thank you for a very wonderful presentation. It helps us at the other end really understand the decision-making process, and I thank you. The

plasma industry has always been very honest about that, and I thank you for -- you know, the industry for its past presentations and you for this one.

I was just wondering. Obviously the development costs are a primary issue here, and oftentimes are the make or break point. One of the things that you heard from the previous presentation is that, you know -- and obviously that is available through the FDA and also through the NIH are small business initiative grants and some of the financial incentives that would go into making for instance a rare product, a product for a rare disorder. Certainly less altruistic if you will, and a little bit more of a green light rather than a red light project. The issue of harmonization is also something we are going to be discussing here.

Have you as a company ever redone these analyses looking at the relative impact of, one, small business initiative grant; two, the incentives present, you know, through the FDA for orphan drugs; and, three, the potential for a different clinical design or regulatory harmonization to impact on the up-front costs in order to allow these projects to go ahead. Because obviously these are all the issues we are going to be discussing here, and understanding from industry which of these issues actually have the greatest impact I think helps us and hopefully help the

regulatory bodies proceed.

DR. WALTON: Thanks for the comments. To my knowledge and in fact there is a history to our organization of precursor organizations I can’t answer this accurately, but to my knowledge I don’t believe we have redone the analyses on the basis of small industry incentives. Most certainly we would have considered orphan drug programs and any feedback to change the initial assumptions with respect to the clinical trial development costs most certainly. So that develops those as you develop your assumptions and have your discussions with the regulatory bodies and you refine your input. But as far as the first case, I am not aware of a situation where we have, but what I would say is that on a going-forward basis absolutely we would look at that. If we qualified for any of those programs we would certain look and run that analysis. It would be --- of course.

DR. DiMICHELE: Thank you, because in my opinion that would be actually very helpful, and -- you know, because all of the things that we are looking at would certainly appear to me, a non-business person, to really decrease the up-front costs, and by decreasing your development costs and actually minimizing risks to shareholders by, you know, allowing some subsidy. So I think that may change your ratios a little bit. Thank you.

DR. WEINSTEIN: Jerry.

DR. HOLMBERG: Yes. Thanks for this clear presentation. The question that I have, when looking at your economic model and the cost comparison between the plasma industry and the pharmaceutical industry, I noticed two things that stand out. Primarily you say the majority of new therapy development is involved in R&D and marketing, and then also a big hunk of your expenses involve raw material.

First of all, I have two questions. When you see such a large amount of money for the raw material, how do you analyze that in comparison here in the United States in comparison to other countries where maybe the plasma industry more in a volunteer market mode than in a remuneration mode that we have in the United States here? Secondly, if you develop such a orphan plasma therapy it would appear to me that the market would be pulling versus you having to go out and push the market, and so the value would be a pull versus a push; and how would that affect your model?

DR. WALTON: Can you repeat the second question again?

DR. HOLMBERG: Well, the second question was basically the push and pull.

DR. WALTON: Okay.

DR. HOLMBERG: In a push and pull, you know, you would basically have to -- when you are generating the market you are really developing a lot in the marketing tools to go

out there and convince the industry that they need this. Here we have the physicians, the patients who know that there is a need, and so you have a pull from the physician. So to me it would appear you wouldn't need to invest as much money in the marketing. How would that affect your models?

DR. WALTON: Yes. Look, I agree with your second point, and it would have a very clear impact on the model by reducing the cost component, and it would positively impact the outcome to not have to invest in significant pre- and post-marketing expenses.

The first question, regardless of whether you have donor fees involved, cost of plasma in some of the markets that are not traded in the same manner that that is done in the United States is still quite high. The costs come from the infrastructure to collect, testing the serological as well as --- testing, the logistics of handling of plasma. It is a very difficult raw material because all of your costs are up front. So regardless of whether you have donors centers as we use in the United States or some other regions where the donors are not given a fee for donating plasma, the costs are still quite high. There is not a significant difference, maybe a 10 or 15 percent difference, and in fact in some countries where they are fully on a donation system plasma costs may be in fact higher than the United States because of the scale of it. We collect an awful lot of

plasma here, and that does enable us to bring costs down. The other issue with this is your cash flow when you collect that raw material is often six months or 12 months ahead of the product hitting the shelves and going through your system because you have to pay for it prior to starting the process. You have to hold it, you have to manufacture it, and you have to run through the full cycle before the product is available, and that drives the cost of raw materials to the levels that I showed there, which are quite high.

DR. WEINSTEIN: Let's see. I think perhaps we will hold some of these questions for the panel discussion we will have.

IPFA Perspective

Clive Dash, MD

DR. WEINSTEIN: Our next speaker is Dr. Clive Dash. He is the Medical Director of the Bio Products Laboratory, and he will talk about current challenges to product development from the perspective of the International Plasma Fractionation Association. His presentation will deal with some of the practical challenges that fractionaters face when having to contend with different international clinical trial requirements, finding willing patients, and getting reimbursement for these products.

(Adjusting equipment.)

DR. DASH: Well, good morning, ladies and

gentlemen. It is my great pleasure to represent IPFA at this presentation. A number of people from IPFA member associations are in the audience, notably --- who is our executive director.

(Slide.)

You will see that he is in his spare time doing a bit of travel agency work because subliminally you will have a picture on the back of the slide there of Amsterdam where he is based. So he is encouraging you to take a holiday vacation in Amsterdam.

(Slide.)

What I would like to do in first in this presentation is introduce you to IPFA for people that don’t know anything about IPFA, and then try to put into some sort of context the way in which our member associations work. I am please to say if you want a short summary at the beginning, as is traditional of course in scientific publications, the three previous speakers have covered many of the points that I will make; and there are not a lot of differences, although there are some between what I will say and what previous speakers have said.

The International Plasma Fractionation Association stems out of the European Plasma Fractionation Association a few months ago. We are made up of not-for-profit organizations scattered around the world. Formerly they were

based in Europe, but we do operate by and large in most countries in a competitive and commercial environment. So we are up against if you like, in the nicest possible way of course, people represented by Paul, our previous speaker, and so on. But we are generally ver small or small to medium-sized enterprises, so that takes us apart from the more international organizations. We stem from primarily national fractionators, and I an certainly endorse what Paul was saying just now that the cost of collecting plasma even for a not-for-profit organization where there is no payment for collection is basically the same. There is not much difference. It is the infrastructure. It's the cost of doing it. We still have that enormous cost, which I will come to in a minute, on the raw material.

Now because we were national fractionators predominantly in the past -- and some still are -- we had, if you like, a remit to satisfy the needs of patients in our localities. Because we were not-for-profit organizations, we didn't historically have to go through the same sort of models that Paul has just been describing to you, but increasingly we are doing that. We have to do that to survive. Because of the cost of heath care in different countries, the support, if you like, from sponsors, which may be, for instance, the local Red Cross or government agencies, is diminishing very rapidly year on year.

(Slide.)

Now we clearly have to comply with all the regulatory requirements. Because of that and other economic issues, if you like, the withdrawal of some of our traditional sponsors, we have to become more international; and most of us are now putting our feelers outside of our own national boundaries into other parts of the world. We have to do the same CMC requirements. We have to do the same clinical trials. There is no difference. There is no argument about that, and so if you think about Paul's model and apply it in the 21st century for membership, then we all have the same, if you like, difficulty in raising the capital and the cash flow in order to support the development of new products and the clinical trials. Some of us have experience with discussions with the FDA and working with the FDA as well as the European agencies. Unfortunately, not everyone could participate in this meeting, but there are quite a number of people here from our member associations.

(Slide.)

I will just put up just a couple of slides now to illustrate that some of the membership in Europe, this is just confined to the European Union now, some of our members have national products. If you work through these as has been mentioned before, factor VII, there are two of the members in Europe have factor seven products, and each

distribute those products in one country each. Factor XI, again two members distribute factor XI, one country each. Protein C, just one organization manufactures a protein C concentrate just marketed in one country. Antithrombin, a little bit more prevalent, but only slightly; three members, one country each.

(Slide.)

If we move on to the IGG products, then we have specifics again. CMV, one member, one country; rabies, one member, one country. Interestingly enough, that is the UK, where rabies has not been seen for a long time; but I think some of our military were passing around the world and liable to get caught up with rabies as well as other things. Rubella, two members, one country each; hepatitis B intramuscularly, similarly; varicella-Zoster, three members, one country each; intravenous hep B, four members, more prevalent, one country each; and tetanus, more or less the same. So that kind of gives you a flavor that scattered around the European Union there are some of these products that have been mentioned earlier today that are available for certain patients.

Fibrinogen was mentioned earlier. A number of our members are working on fibrin ---, and as part of that of course fibrinogen is an integral component, and that is also available in some countries.

(Slide.)

The national markets really are too small now our sponsorship, if you like, is diminishing, so we are having to look elsewhere. But we do find that there are some limitations in licensure internationally. Sometimes patent issues cause us difficulties. The fear of litigation in certain localities is another major issue to some of our members. The lack of regulatory harmonization has already been mentioned several times, and the changes in health economics also have an adverse effect on the way we perhaps are looking at the way we do our products in the future.

(Slide.)

There is an example here which covers a number of different points I think. One of our members who has now closed down their fractionation facility, the Finnish Red Cross is still collecting some blood there, but they don't fractionate their own plasma anymore. They developed an apotransferrin product. There were two patients in Finland with congenital deficiency. There are several individuals in the US. Their fractionation facility has now been transferred -- for major products, transferred to Sanquin, which is the Dutch and Belgium organization. One issue I guess that we have to think about that hasn't been raised this morning is in a situation like this there is the issue of technology transfer and what that might bring and what the

cost of that might involve, and at the moment an uncertainty about the trial requirements if we wanted to expand into a national area with that particular product.

(Slide.)

Traditionally as national organizations our membership has had limited number of patients, and even if you take primary immune deficiency as an example where chronic replacement treatment is present. I have avoided factor VIII and factor IX because many parts of Europe now recombinant therapies have largely displaced plasma-derived ones. With primary immune deficiency, the patients have a chronic replacement treatment, as you know, but they are perhaps unwilling to switch from the current product that they have been using for goodness knows how many years perhaps to a new product. If they switch, they go into a clinical trial. What does it mean to them? It means that they have inevitably more visits to the hospitals, many more venepunctures to comply with the requirements, they have more paperwork for themselves, and all this interferes with their life and work style.

(Slide.)

There is also within a particular geographic location generally a competition for willing patients. So those that are willing are highly competed for by a number of organizations developing similar products. This is perhaps

not the really rare conditions, but still products that we make from plasma. The duration of the follow-up can be a disincentive to patients, and overall in Europe I don’t think there is any personal incentive to the patients to take part in the trial. They are almost certainly doing it on a high degree of altruism when they do that. How to do a comparative study in patients on long-term treatment poses another difficulty. As part of some earlier discussions with the European regulators, we suggested that some proactive pharmacovigilance might be a good way forward. I was pleased to hear this morning several of the speakers making this particular point. We have heard it before also, the high cost of clinical trials. The cost of a clinical trial, as I said, run by an IPFA member is the same as the cost of a clinical trial run by a for-profit organization. We have a small organization, small --- organization, so the proportionate amount of money spent on developing products is much higher.

(Slide.)

If we look forward, as you might be thinking, "Why don’t you rush out into the international markets and distribute your products there?" as traditionally national organizations we do not have an international infrastructure. So we have to find other ways of distributing our products outside of our own national boundaries. You have heard a

tremendous amount from Paul about the economics of plasma fractionation, and this also leads on to another point which hasn't been mentioned yet this morning. But if we are taking a new protein, let's say, for a rare condition out of plasma, this might sound quite easy on the face of it; but there are potential complications, and the potential complications are depending on where that protein lies in the process from the beginning to the end of the fractionation will perhaps impact upon other products that are already licensed. So if you are taking something out, a protein out of an intermediate product, then you might affect the other licensed product already coming from that particular plasma. Therefore, that could be an affect on the licensing status of the well-established product, and that is another fact that we have to take into consideration when we are working out the economics of whether to develop a new protein for any condition, whether it is rare or less rare.

(Slide.)

Clearly as has already been said, we need enormous collaboration between patient organizations to help overcome some of the issues that I have mentioned, physicians in order that they can give the right support and work according to the current TCP regulations, the regulators for reasons as already mentioned, and amongst ourselves. I think if you consider a product for a rare condition it is not -- and may

require relatively small total number of patients let us assume, it is not necessarily that much cheaper to do that than to run a bigger trial where patients are more numerous. The reason is that the costs of trials do not run proportionate to the number of patients. They are partly generated along that line, but perhaps more importantly the number of centers. So if you have patients scattered very sparsely over a large number of centers and you have to recruit all those large number of centers, that disproportionately pushes up the cost per patient.

(Slide.)

Touched upon before, but perhaps in Europe we have more socialized medicine, although it is not totally socialized across Europe. But the key issue that I think keeps coming back to us when we go through these scenarios is if we are really, even if we are not a for-profit organization, trying to, if you like, break even, will the purchasers actually be prepared to pay the price for that product for that rare condition. The cost of producing it is, as I have said before, is the same whether you are a big organization or a small organization by and large. The pressure on pushing prices down of all products, pharmaceuticals as well as plasma-derived products, across Europe is enormous, and if you come in with a new product the risk is that the real cost, which should equal the price, if

you like, for a not-for-profit organization, is still going to be too high for the purchasers to -- and the purchasers have in many parts of Europe the final say on what the patients receive.

(Slide.)

So in conclusion, we have many challenges. Most of them are the same I would say as for the other larger organizations. The resources available are limited, more limited, and the investments required are probably more limited, and they are getting more tight as years go on. We have a difficulty sometimes with patient populations nationally and we have had to expand outside our national boundaries in recent years, and we have to face the availability and willingness in those patients to take part in the long-term trials when they are perhaps, for some products anyway, receiving product already on a long-term basis so there is no real incentive. We would like to have more regulating harmonization and we would like to move towards international commercialization as other companies have done in the past. Proactive pharmacovigilance I think probably works quite well particularly with rare conditions because the patients are almost known as individuals, even with confidentiality and so on, even I would say to most of the manufacturers of the product. So it is relatively easier I think to track those down and to keep a good trace on what

is happening to them after the product has been allowed out into the market. As I said before, one point that has not been raised earlier today is the potential impact upon taking a new protein out of an intermediate during the process of fractionation and what that might impact on already-licensed products already downstream. Thank you very much.

(Applause.)

DR. WEINSTEIN: So again we have a few moments for questions if you would like to raise any. Okay. Okay, Donna.

DR. DiMICHELE: Yes. Donna DiMichele. Thank you again for this presentation. It was very informative as well and brings a different perspective. One of your concerns is the willingness of these patients to participate as clinical trial subjects. I think that there may be a difference, I mean, and I think this is very pertinent to an expansion into an international market because there certainly might be a difference in the willingness to participate maybe based on what you have heard already between those patients who have no access to product and those patients who already have access to product. So there is intent among the national organization, national participants in your organization to expand into international markets, I think you may find you have plenty of subjects if clinical trials are redesigned to participate, if that removes that concern.

The second is about purchasers. We obviously are going to have some -- hopefully some purchaser representation later on But the other thing to consider is that when a purchaser, commercial purchaser, has to purchase for a single patient or for two patients, et cetera, although the cost per patient is high, sometimes -- sometimes -- they can still remain below the radar. You know, below the radar screen in terms of a blimp in cost; but that climate is changing, too, and I am not sure we can say that most definitely. But thank you.

DR. DASH: I will just a couple of comments. I think we invented radar, and I think in the UK the radar is so sensitive that we are finding it really difficult now to get below it. But I think you are right. I mean, we have had problems with factor VIII, factor IX primary immune deficiency patients who are on long-term treatment, no incentive for them to change in most countries in Europe. It will be different I am sure for the other conditions we mentioned this morning where there is no other satisfactory treatment.

Developing Biological Therapeutics for Rare Plasma Protein Disorders

Toby Silverman, MD

DR. WEINSTEIN: Our next speaker is Dr. Toby Silverman. She is the Chief of the Clinical Review Branch in

the Office of Blood at CBER, and she will discuss developing biological therapeutics for rare plasma protein disorders. Her presentation will focus on the usual standards that FDA applies for the licensure of products. In later presentations we will discuss how products for very small populations fit into this overall framework. Toby.

DR. SILVERMAN: Well, Mark has given my first slide. I want to discuss here the usual standards that FDA applies for either licensure or approval of drugs, and it is against this background that discussions this afternoon will take place about how drugs or biologics for rare disorders might meet the standards that I am going to outline this morning.

(Slide.)

One needs to take a step back and look at where these standards came from. In 1938 we had the birth of the modern pharmaceutical industry with was based on research and development of potent new medicines. There was a requirement to test drugs for safety alone before marketing. There was no requirement for companies to inform the FDA of medical experiments for new drugs before actually conducting the experiments, and physicians could administer drugs without consent to an unlimited number of patients as long as the work was deemed experimental. Obviously this would not meet current standards. In the 1950s and into the 1960s there

were a number of problems with drug development, including chloramphenicol and most famously thalidomide.

(Slide.)

This lead to a change in the legislation in 1962, an amendment to the Federal Food, Drug, and Cosmetic Act was enacted to add the requirement for demonstration of effectiveness for drugs and biological products basically to assess benefit-to-risk rations. Then as I said, prior to 1962, manufacturers were required to demonstrate only safety.

(Slide.)

Now what is the quantity of evidence generally necessary to support effectiveness? This standard is outline in section 505(d) of the Food, Drug, and Cosmetic Act, where substantial evidence is defined as evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling. Now I heard earlier today a number of people say that they would like to have adequate dosing guidelines, they would like to know a risk-to-benefit ratio for their patients, they would like to know how to use drugs. These standards are designed to achieve that goal.

(Slide.)

This standard has been interpreted by FDA to mean generally two adequate and well-controlled studies, each convincing in its own right, is necessary to establish effectiveness.

(Slide.)

However, on occasion FDA has relied on pertinent information from other adequate and well-controlled studies of a drug -- for example, studies of other doses, other regimens, other states of disease in other populations of different endpoints -- to support a single adequate and well-controlled study demonstrating effectiveness of a new use for a drug.

(Slide.)

FDA has relied on only a single adequate and well-controlled efficacy study to support approval. But this is generally only in cases in which a single, multi-center study of excellent design has provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds. Now this is obviously a very difficult standard for rare plasma disorders, so again later this afternoon there will be discussion about how to address this standard for these disorders.

(Slide.)

The FDAMA, the modernization act, amended section 115(a), amended section 505(d) of the act to say that FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. Well, that is a judgement call obviously.

(Slide.)

Now the Public Health Service Act, under which most of these products will lie, licenses for biologics are issued upon showing that the products meet standards designed to ensure continued safety, purity, and potency. Potency being defined as specific ability of the product demonstrated in laboratory tests or adequately-controlled clinical data to effect a given result.

(Slide.)

Now proof of effectiveness consists of controlled investigations as defined in the provision for adequate and well-controlled studies, unless these requirements are waived as not applicable to the biologic product or not essential to the validity of the study.

(Slide.)

Now in the Code of Federal Regulations at 601.25(d)(2) there are provisions for alternative methods to

substantial effectiveness acceptable for biological products, and among these specifically listed in this section are serologic response data, and one example is -- one example is serological response data, provided that a previously-accepted correlation with conical effectiveness exists.

(Slide.)

What is the scientific basis for the regulatory requirement? Well, there may be unanticipated, undetected, systematic biases. There is inherent variability in biological systems that may result in a finding of efficacy by chance alone. Results may be driven by outcomes form one center and unfortunately, on occasion, scientific fraud.

(Slide.)

Now, whether to rely on a single adequate and well-controlled study is of course, as I have mentioned earlier, a matter of judgement, and it is apparent a conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. The endpoints of course of mortality, irreversible morbidity, prevention of disease with potentially serious outcomes are obviously all endpoints for consideration.

(Slide.)

So what makes a single study okay? Well, a large, multi-center study in which no one site provides a disproportionate percentage of the subjects would meet the

standard. A study where there is consistency across subsets in large trials with relatively broad entry criteria. That does not pertain here. These are small populations. Multiple endpoints involving different events, and statistically very persuasive findings.

(Slide.)

There are some caveats. One must always consider the possibility of an incorrect outcome, and this of course is very important if one is looking at only a single study, and the available data must be examined for their potential to support or undercut the results.

(Slide.)

So how do you get from a good idea to market? Well, everyone in the room knows that there are several phases to studies. We meet often, FDA meets often, with companies and investigators at the pre-IND phase to outline clinical trial designs, CMC issues, et cetera, preclinical work that is needed. Under IND, investigational new drug application, the ususal course is to go through phase I, phase II, phase III, leading to licensure, and then often phase IV commitments or post-marketing commitments are made.

(Slide.)

Clinical trials. A clinical trial is a prospective study comparing the effect of interventions against some control in human beings. The purpose is to distinguish the

effect of the drug or biologic form other influences, such as spontaneous change, placebo effect, or biased observation.

(Slide.)

One assesses efficacy by comparing outcomes in a group receiving the drug to the outcome in groups treated with a control. Once tries to isolate receipt or non-receipt of the drug or biologic as the only important difference between the groups; and the gold standard, one which will be difficult here, is a randomized well-controlled trial where balance is ensured by the randomization process.

(Slide.)

Again the usual course in phase I, phase I trails are generally run in normal volunteers. They may have no benefit from the drug or biologic. One may run phase I studies in patients for whom the agent is intended. This population may have more advanced disease than the ultimate intended population. In later phases of the study, one studies the intended population, and one is left with the question of how to extrapolate data from patients in a trial to the more general population. It is also necessary to include groups previously under-represented in studies, such as women, children, or the elderly.

(Slide.)

How does one choose an appropriate control for studies? The proper choice for a control is necessary in

order to determine if the drug works. There are different types of controls. In the right setting one might run a placebo controlled trial, which is the clearest way to demonstrate efficacy. Obviously that may be difficult for some of the populations that we are discussing today. One might have as a control an approved therapy, in which case one would design a trial to show either superiority to the active control or equivalence to the active control. One might evaluate different doses of the same agent to evaluate dose response; and, last, one might consider historical controls.

(Slide.)

If there is a known effective treatment, some groups have raised concerns about the use of a placebo, even if there is no lasting harm. Of course it would be unethical to withhold a known effective treatment if withholding the effective treatment would do irreversible harm. In some cases, one could consider the addition of a placebo or the active agent to a standard of care where one would compare the standard of care plus the agent to the standard of care plus the placebo.

(Slide.)

Non-inferiority trials attempt to show efficacy by showing a new treatment is as effective as a known effective therapy treatment. One demonstrates that a new agent is not

worse than the control by some narrow margin which remains to be defined.

(Slide.)

There are some disadvantages to non-inferiority trials. Assay sensitivity, if the active control does not show consistent results, it is very difficult or virtually impossible to reach firm conclusions about whether the new treatment is as effective as the old treatment; and, unfortunately, non-inferiority trials require very large sample sizes to rule out small degrees of inferiority. Again, not an option, not a readily-available option, for these small populations.

(Slide.)

The choice of the endpoint depends on the phase of development, the clinical setting, and the intended effect of the drug. There may be many choices of endpoint; range of safety in phase I, and activity and effect, especially in phase II. Generally, for approval for most drugs or biologics an efficacy endpoint should be a clinical benefit or be a validated surrogate that best measures the clinical benefit of interest. Now, I heard discussion about accelerated approval, and that is certainly a consideration for some of drugs, in which case the surrogate endpoint might very well be an -- or would be an unvalidated surrogate that is likely to correlate with the clinical benefit.

(Slide.)

Surrogate markers are used to diagnose disease or evaluate patient response to treatment. The effect on the surrogate marker should reflect the equivalent effect on disease or true clinical endpoint of interest. It has advantages, as has been noted earlier. It is easier and faster to measure a surrogate than to measure an actual clinical benefit. The surrogate may occur in more patients and may decrease the cost of the study. There are some disadvantages, however. If the surrogate does not correlate, it may result in an overestimation or underestimation of the true effect.

(Slide.)

There are some confounding factors to consider in clinical trial design as well. These include bias, regression to the mean, imbalance between study arms for studies that have two arms, dropouts, and multiple endpoints.

(Slide.)

The appropriateness of the study design for the indication is very important in these considerations. Randomized, controls, a well-defined selection of subjects, appropriate endpoints and appropriate choice of control groups are all very important to determining efficacy.

(Slide.)

In the final analysis, though, all of these

comments and considerations are aimed at evaluating whether the results show that the product is safe under the conditions of use in the proposed labeling, and, the second question, do the results of well-controlled studies provide substantial evidence of effectiveness so that treating physicians understand dosing, understand the effect of the product, and can use the product safely. Thank you.

(Applause.)

DR. WEINSTEIN: Again we have time for a few questions. We again would also have time at the end of the panel discussion for a question period. I think, Donna, do you --?

DR. DiMICHELE: Thank you for that. You know one of the things that you mentioned and spoke quite a bit about is surrogate markers, and obviously one of the toughest markers for a clinical trial is clinical efficacy, because as clinicians we really haven’t developed good markers for clinical efficacy for you all to use as endpoints. You mentioned surrogate markers, and I was wondering if maybe in the discussion we could explore that a little bit more. For instance, such as plasma levels, you know, understanding that there may be some correlation between clinical efficacy and plasma or serum levels of drugs in certain cases, or replacement products, and maybe whether we could explore that a little further.

The second is if you have limitations in clinical trials, which of course for the rare bleeding disorders we would be talking about that in a significant way, I would be interested in your opinion as a regulatory as to what would be needed in phase IV pharmacal surveillance post-licensure in an effort to assure the FDA with a small clinical trial size that we would continue to do the best surveillance possible and what are the elements of that surveillance.

You don’t need to necessarily answer these questions now, or if you have some thoughts that would be good. Maybe we can discuss it more in the discussion.

DR. SILVERMAN: I think Dr. Jain will be talking about some of these issues as well this afternoon, and I think most of the speakers this afternoon will be discussing some of these issues. It is obviously very difficult, a difficult issue as to what to follow, what to look for. We can talk about plasma levels. This is certainly the endpoint for pivotal trials for factor VIII and factor IX because we understand that surrogate reasonably well. It might very well be a surrogate for some of these other replacement factors as well.

DR. WEINSTEIN: Okay. Keith?

DR. HOOTS: A question about backdoor entries into getting an indication. If for instance we have heard that factor V, there is no likelihood of developing a factor V

concentrate. We don’t presently have a pathogen-attenuated fresh-frozen plasma. How do regulatory agencies look at say trying to develop a solvent detergent or some other pathogen-attenuated fresh-frozen plasma for rare diseases knowing that were you to license it for that indication the broader use would be far beyond a rare indication use? Or maybe you don’t. I mean, maybe that is a politically-charged question that you don’t really want to address, but I think it does present a problem if someone really wants to develop that for that purpose and has the technology. But perhaps is concerned that it may be a detriment for a broader use I guess is what I am asking.

DR. SILVERMAN: Well, as you know we had a solvent detergent-treated pooled plasma product. We have never had a solvent detergent-treated fresh-frozen plasma product. The particular product, the pooled product, had all of the indications for which FFP was licensed, and obviously that would include rare disorders for which no licensed concentrates were available that was specifically on the label. Certainly specifically on the label for fresh-frozen plasma in the circular.

DR. WEINSTEIN: Okay. We will have a 15-minute break. We will reconvene promptly at 10:30 for panel discussion where we will have the speakers at the front of the room.

(Whereupon, a break was taken.)

Open Panel Discussion

Mark Skinner, Session Chair

DR. WEINSTEIN: Panelists, please come to the front and be seated. So we are going to have a panel discussion now. The leader for this panel discussion is Mark Skinner. He is President of the World Federation of Hemophilia. Mark has a long history of involvement with the bleeding disorders community, principally through his work with the National Hemophilia Foundation. Mark is also a member of the Advisory Committee on Blood Safety and Availability. Mark.

MR. SKINNER: Good morning. Before we move into the questions, Mark thought it would be helpful if I just give a bit of a perspective about the role of the international patient organization in addressing the problems that we are talking about here today, so first I just -- this was mentioned by Amy, and this really is -- you know, kind of captures what it is that we have been trying to achieve here in the US.

(Slide.)

In particular, the bullet under item two. Most of the world, and a lot of the developing world, still relies on fresh-frozen plasma, and we know the history and experience when you are relying on non-virally-inactivated products. So the issues were are talking about here today aren’t just

applicable to the US, but we are talking about developing in fact a global market.

(Slide.)

I talk about this in terms of a market because that is what the manufacturers talk about, and I see it really as two-fold. The first is bringing the patients to the marketplace and then bringing the products to the marketplace, and both have to in fact occur in tandem.

(Slide.)

The role of the patients organization really is in the first category, how do we bring the patients to the market. If there aren't patients there in fact is not going to be incentive for development. So the World Hemophilia Federation, which is in fact a federation of 107 member countries scattered around the globe, has a very comprehensive country development program. It all begins with beginning to identify and reach out and find the patients in the countries, educating the patients, and then we move into a laboratory diagnosis program since you can in fact identify them. In fact, WFH publishes a laboratory diagnosis program and manual which in fact includes how to diagnose for rare bleeding disorders. We have an international quality assurance program, and we do workshops and training around the globe at different points in the year to actually train laboratory technicians within countries.

Once you have identified the patients, the next critical step is in fact creating a register of the patients in that country, and that register in fact then provide the important data collection and analysis to try to build the case for support to persuade the governments then to purchase products to treat the individuals with hemophilia and other related bleeding disorders. Depending upon where you are in the globe, it either occurs through a government purchase or a tender, or in the US through changes in the reimbursement coverage.

Specifically as it relates to countries outside the US that work through centralized government purchase and tender programs, most of the tender programs provide some mechanism, either within the tender to purchase for known patients for rare bleeding disorders -- which is in fact why the registry becomes critically important so they can estimate those needs -- or there are special access programs such as there are in Canada and Ireland where the patients that are identified in fact then can access those programs and the government will pay for them outside of the normal tender process in the federal government's purchase.

(Slide.)

So where in fact are the patients in the world? The WFH conducts a global survey every year, and what I am about to show you in fact is unpublished data. We publish

this every year, and the 2005 survey has not yet been published. This year we have expanded our survey, and in fact now 96 of our 107 member countries in fact report, and of those 107, 61 of them in fact are now reporting data for other bleeding disorders. The sources for our data come from a collection of sources. Those countries which in fact have national patient registries, and the others are conducted through surveys of the hemophilia treatment centers, and then in fact there are a number of others that have a combined process or in fact are the patient registries in the country where the healthcare system is a little bit less established. But the bottom line is that our registry now shows 10,496 patients globally that have some other type of inheritable bleeding disorder other than hemophilia A/B and Von Willebrand disease.

(Slide.)

I thought it would be interesting just to show you quickly at least what the data shows where the countries are reporting that they in fact have them, and I have put on the screen the countries where patients are reporting more than 100 diagnoses. What I don’t have and what our survey does not collect is in fact what the actual diagnosis is by country, but what it does show is there is a fair amount of concentration among the established care countries. There are a few other countries where there is some hereditary

precedents and some particular concentrations within the ethnicity of a population that bring about the numbers, but there is in fact a relatively large population. As the World Federation has begun to tackle this issue along with the National Hemophilia Foundation, we have been talking about this more. In fact, we are going to be publishing a treatment guide for patients with rare bleeding disorders which will be out later this year as well. So the question then becomes if we build it, if we find the patients, if we persuade the governments to include treatments for rare bleeding disorders within their national tender and purchasing programs, will in fact the companies come.

(Slide.)

Which is in fact the second part of the equation in bringing the products to the market. I did have an opportunity to see the presentations in the first section before today. So as I was reading through them there were two statements that stuck out, both in Dr. Dash's and Dr. Walton's presentations, and they really aren't dissimilar. I mean the first is will the healthcare purchasers agreed to purchase the need products for the needy patients, and the second is a 15-fold increase in price would be required to break even. You will recall this. I think it was in case C, which related to the rare bleeding disorders. Both of those are certainly daunting and challenging goals,

and there are some differences, although there are also some similarities, between the two market statements. I think we have already heard that the non-profit companies, the national manufacturers, in fact do produce a number of the rare bleeding disorder products, factor V, factor IX, factor XIII products, which aren't currently available or licensed in the US; and the other part of the equation is what is the incentive to develop products for those, for the other rare plasma disorders and bleeding disorders. So I just wanted to provide that sort of historical background, that if we do our part on the side of the patients, if we find the patients, if we train the clinicians, if we provide the diagnosis and we persuade the governments to express an interest in purchasing the products, will the manufacturers in fact come to the table, and what will it take for them to move forward and produce the products.

(Slide.)

So what I wanted to do is to now move into the questions, and I had a couple of questions that I wanted to ask the panel and then open it up to the actual discussion. The first question that I was interested in asking is, and I wanted to direct this to Drs. Walton and Dash, is that as you think back on your presentations and you think about all the subjects that we will be discussing today, there is certainly a number of ideas that have been put forward. But if you

could pick one single initiative for us to pursue, for us as a group to coalesce around by the end of the day tomorrow in terms of trying to advance forward, what do believe would be the single most important thing that could be the outcome of this meeting to advance access to care and to bring products to market?

DR. WALTON: I think given -- there are a lot of factors of course, but given the context of the meeting and the hosts of the meeting, I think the issue of the cost and style of clinical trials, and mechanisms to not compromise of course the objectives of the regulatory agencies in conducting, but for example we have heard discussion of harmonization and utilization perhaps in the case of drugs that are registered and have a history of use in jurisdictions outside the United States, et cetera. I think the focus on being able to reduce that barrier for manufacture would have a significant impact, and the reason I state that, if you recall in my presentation that one of the things that has a negative impact on the model from a cash flow standpoint is the up-front costs. All of these costs occur up front before you get to a positive cash flow case, and their impact is amplified in the model financially. So that would be a focus if there was a way without compromising safety and the other objectives to reduce that investment cost.

MR. SKINNER: Dr. Dash?

DR. DASH: Yes, I go along with that, but I think the issue would be having some form of guarantee that when we get to the clinical trial stage, whatever it is, the money that we would have expended up to that, which is not small, is worthwhile. So to embark upon this route if you are leaving home to go on this route to get licensure, we would only embark upon it if we had enough money to pay for the whole train fare, air flight, or whatever it was. So that if the trials were guaranteed to be of a certain nature, and sometimes we don’t always know what we are going to be aiming for when we are starting to think about developing a new product, then we might embark upon that road; but I think otherwise it would be extremely difficult to do so.

DR. WALTON: I would have given that answer, but you said I could only give one.

(Laughter.)

MR. SKINNER: So in essence then I think we are going to be hearing from the folks from CMS. I think Dr. Bowman is presenting later the Medicare or the private care reimbursement systems that have to move in anticipation of products coming to market, which is not something that in fact is customary in the US marketplace as well, which perhaps is a separate challenge that we may not probe in detail.

The second question that I was interested in really is more for Tony and the clinicians, is -- and the manufacturers may have a position on this as well. If we are talking about an expedited or a streamlined clinical trial process, something that is less akin than what we are familiar with and perhaps less rigorous than what we are familiar with, does that in the patient's mind create an additional level of risk, that the level of safety or the level of risk is in fact greater than other products, and is there a challenge in overcoming that?

The corollary question to the manufacturers is, and I have heard it in two of the previous presentations, was a reference to the fear of litigation. That if in fact that there is additional risk on the part of the patients, or at least they are perceiving there is additional risks, or perhaps don't perceive it but in fact something ultimately happens, is the fear of litigation an impediment to the marketplace that perhaps nobody in this room has the ability to deal with, but that we also have to find a way to address to bring the products. So I don't know if the doctors or, Tony, you want to respond.

MR. CASTALDO: I will go ahead and go first. Those are some very interesting questions, and we grapple with those, believe it or not, as a patient organization on a day-to-day basis understanding the fact that the lead therapy for

our condition is a plasma-derived product. I guess the answer to your question almost bets additional questions, and that is one of the things that we are here today to hear about and hopefully see if there are some additional ideas that could be put forth. I guess for every individual indication the circumstances are very different, and I will put aside efficacy for a moment and just talk about safety.

Perhaps our view is naive because we indeed are not specifically statistical methodology experts with respect to surveillance data and so forth, but when we step back from our limited vantage point and look at the -- what would seem to us to be the cumulative safety data in very sophisticated Western European countries for the plasma-derived product C-1 inhibitor concentrate, we I think as a patient community would be ready to step forward and say what I mentioned in my talk. That is we firmly knowing these scientists as we do because we participate in all the HAE meetings and have for the past five years, we feel that the network is in place -- and perhaps the surveillance isn’t as methodologically pure as we might want it to be, but we feel that the confluence of data that would be available at this juncture from Western Europe, from our own personal importation usage here -- and all of our patients certainly are screened for sero conversion -- we feel that the preponderance of evidence is fairly unequivocal and that if there was a problem with viral

-- again, a sero conversion or any other issue with the medicine that it would have been reported either by the companies or by the clinicians. Because, again, what we have in Europe that we don't have here in the United States, and we hope to develop this as our organization goes from a volunteer fledgling one hopefully to a more sophisticated situation, we hope to develop the network of scientists and physicians that are pretty much dedicated to looking at the HAE pathophysiology and all the different treatment ramifications. That has been going on in Western Europe for well over a decade. So, again, the bottom line is for us we don't feel that -- we feel the safety at this juncture is fairly well described, and I think it is fair to say -- and this is certainly the consensus of the Chicago meeting of our patient group in April, that we are very comfortable right now with the current technology for spectra viral inactivation and the data that is available for that particular product.

DR. PEYVANDI: I think to resolve this problem there are two main goals. The first one as was mentioned, the registry and the other would be the international registry. Because if you go through the literature you really can find very fractionated data on the genetic study and the phenotype study, but we have no data or information on the treatment, on the side effects, on the safety,

security. I think really this time is a time we have to put all the information together, and tomorrow we show what is going to be the focus of the RSDH for the international registry containing all the information together.

The second point I think is very important is the internationalization of all the studies and also the producer and the drug companies for -- how I can explain -- the commercial point of view has to be changed. Answering to your point, I think we need to know how many patients are distributed, how in world, and how many persons of this government there are already importing tho product. Because 70 percent of the rare bleeding disorder are distributed not in Europe and in the United States, and 30 or 20 percent of these patients, they are receiving the plasma, but they are in such an economic condition that the import of factor VIII or factor IX is already available in that country. That is the reason I don’t think so for both clinical trials and for commercial point of view we have to focus absolutely on the international type of information and getting involved the patients in these countries.

MR. SKINNER: Dr. Shapiro.

DR. SHAPIRO: Mark, I think if I heard you correctly what you talked about is does this represent an increased risk to the patient to participate in a clinical trial. I think from my experience with my patients in

discussing this, specifically from plasminigin deficiency, these individuals really don't have anything that is efficacious at this point in time. The risk to them is getting something that is efficacious. I don't think that they perceive participating in a clinical trial a risk if they have access to a product that may help treat their symptoms. I think we also have to kind of retool our thinking with some of these disorders. It is not like we are talking about looking at clinical efficacy and safety from the standpoint of treating hypertension with a new drug for hypertension. We are talking about for most of these issues replacing something that they are deficient in, and so it may be as simple as documenting getting levels in patients and showing regression or the abating of symptoms that these patients have in association with their disease. Clinical significance for that, randomized controls for patients when you have a therapy that can be efficacious, it is difficult to conceive of withholding therapy from someone, you know, who could lose their sight or their hearing. You can use historical data for some of these things.

MR. SKINNER: Thank you.

DR. SILVERMAN: Obviously this is going to be a matter of consent for patients. I want to echo what Dr. Shapiro has said, which is that for many of these people there may be no alternatives. In which case, you have a very

different benefit-risk-ratio than for patients for whom there may be alternatives. Again, it is an issue of consent and outlining for people what their therapeutic options really are.

MR. SKINNER: I know it may have been somewhat of a rhetorical question, I expected the answer. But I think it is important to articulate the difference of risk perception and access to care versus patients with rare disorders as opposed to the very rare disorders, and that in fact it is a different level of analysis. The other piece before we open it up, I am very curious about the aspect of litigation and whether the fear of litigation in the US is a concern to product development, how big a concern it is, and whether that in fact is -- makes it a non-starter to even have an interest in pursuing the product development. Yes, both for you and Dr. Dash.

DR. DASH: I will make a comment on that if I may. I know of at least one situation where a product which had previously been coming into the US was decided by power that decide these things that that should not be allowed because of the fear of potential litigation. There had been no problems up to that stage, but this was a fear that was expressed and it was expressed at such a high level the product would not be imported into the US. So it has happened in at least one occasion, probably more. There are

3,000 miles; there is a big perception.

DR. WALTON: I will only make a general comment. I think in our business one of the decision-making issues that we always face is the risk of litigation and product liability, but I don’t think it outweighs other issues that we would look at in other rare or non-rare disease cases. So obviously we want to avoid that and we have the business practices in place to consider this situation, but I don’t think it is an outstanding issue in this situation. I think it depends of course on the individual case, the drug, et cetera, but I don’t think it is something that think would be a major barrier to our support of these programs.

MR. SKINNER: Thank you.

DR. SHAPIRO: I don’t speak from the manufacturer’s end, but having a conversation with a manufacturer from Europe it was mentioned to me that that was a concern with the United States, that we are very litiginous.

MR. SKINNER: And I have heard the concern as well in conversations.

DR. SHAPIRO: I am telling a lawyer that, right?

MR. SKINNER: No, no, don’t hold it against me that I am a lawyer as well. Maybe it is the lawyer that made me ask the question, but it is often in the back of people’s minds and certainly when we look internationally I have heard the comment outside the US about people coming into the US

market. Yes, Tony?

MR. CASTALDO: Yes. Just one last quick comment again to just give a perspective that may be, you know, a little bit different. It is always fun I think and interesting that there is an eclectic approach taken to certain situations, and I have some background in a different regulatory environment, and it has to do with financial institutions. One of the sort of international catch words for analysis of in terms of analyzing and evaluating a bank examination situation where you go in and you decide what to do to insure the safety and soundness of an institution, the catch word is called the risk focused approach, and I sort of see some applicability here almost to rare disease regulation perhaps. The concept basically is very simple. When you go in and you do an analysis, you look at the inherent risk profile of that institution by analyzing a variety of factors. Then the analysis that is done, the depth, the length, during the examination is commensurate with sort of the risk profile that that institution provides. I think in a way that is kind of what we are talking about here.

I know in Dr. Shapiro’s patient community and in mine we don’t really have an alternative right now. So I think that shifts the risk profile considerably and I think that is indicative of the fact that people are mortgaging their homes and doing whatever they have to do to buy their

one product that can attenuate the underlying pathophysiology and symptoms of their disease.

MR. SKINNER: Thank you. Okay. We will open it up now, and if you can just identify yourself as well as if you have someone specific to answer the question that would be good. So we will open it up.

MR. RICE: Richard Rice. I have a question for Dr. Silverman, and it relates something I have and probably you have thought about over a long period of time, but I think it will have a special applicability as we go into this afternoon’s session. It has to do with surrogate endpoints. We all are aware of the difficult with surrogate endpoints, and the FDA’s position has always been that the surrogate endpoint has to be, quote, "Validate." I would like to ask you what the -- if that is just strictly a judgement issue or whether there in fact are guidelines, or draft guidelines or points to consider about that, and how that specifically relates to drug or biologics that are first in class or the only in class as would apply here later to day.

DR. SILVERMAN: Well, there are several questions that asked in that one. Let me take this into the discussion of fast track, which is I think where you are going and where it probably is best defined. A surrogate fast track incorporates accelerated approval along with some other features. For a surrogate to be acceptable to FDA for a

quite, "standard" approval, even if it is a shortened time line, it has to be validated. For a surrogate endpoint to be acceptable under accelerated approval, a different regulator standard, then it has to correlate -- have a reasonable likelihood of correlating with the endpoint of interest, and it need not be validated prior to approval. There is, however, a back-end requirement under accelerated approval/fast track for subsequent validation of that endpoint.

Now I don’t know if this is the appropriate forum to get into a discussion of what constitutes validation, which I am sure that the statisticians and others would -- I think it is probably the subject of another workshop. No, it is not just a matter of opinion. We can get into a discussion offline, if you will, about what is involved in validation and you can involve the statisticians as well. But for purposes here, no, it is not just a matter of opinion. There are two standards for surrogate endpoints. One for your standard approval, even if it is a shorter time line under a priority review for FDA, and one when it is accelerated approval where the surrogate is not validated. Did I answer all three questions?

MR. RICE: I think close.

DR. SILVERMAN: There were a lot of questions there.

MR. RICE: Yes, I admit that. Yes, a lot embedded in the one question. But the issue really of what constitutes validation and what constitutes a -- I forget the phrase you used, but reasonable expectation that they correlate in some way

DR. SILVERMAN: I think that maybe we should take this up as a subject of another workshop. It may be a useful -- I think it is going to take that much discussion.

MR. : --- from --- in France. I want just to add a small comment on the safety and litigation issue that was debated previously. I think that the plasma-derived products that are addressing rare bleeding disorders are --- plasma-derived products, and all the companies that are dealing with this matter, whether they are not-for-profit or for-profit, has gained a lot of knowledge, knowhow, and ethics and obligations regarding the safety of the products. I think that among the topics that could be assessed for the present value of whatsoever if the product is not carrying enough safety in terms of guidelines, requirements, it will not be pushed to the market whatever the --- present value. So I think that all products that will be presented during this workshop has been carefully assessed inside the companies and together with the regulatory authorities to insure that this level of safety is a prerequisite. So I think that it is much beyond the question of the

investigation ---.

MR. SKINNER: Dr. Weinstein, did you have a question? No, Jay. I'm sorry.

MR. EPSTEIN: This is a question for Drs. Dash and Walton. The economic model that you presented really was driven by two things, the up-front costs and the discount rate. With respect to the up-front costs, a lot has been focused on the issue of the cost of the clinical trial, but I wonder if you could also comment on where you see any possible economies related to things like facilities and GNP? And then with respect to the discount rate, Dr. Walton, you explained that that was how a risk assessment was reflected into the model. But I wonder if you could comment a little bit further on what kinds of risks you are talking about, because, you know, clearly the risk of success or non-success terminates. It is not really reflected as an ongoing discount the way the equation is framed, so really those two questions. What can you say about the other major fixed costs, particularly the facilities, and how exactly do you translate a set of risks into the discount rate?

DR. WALTON: This is obviously no standard answer in terms of the up-front costs. It depends again on the product and where it comes out of the fractionation scheme. So the sort of things that we have to consider from an up-front -- from a standpoint of up-front costs, and just to

correct you, there are really three things driving the model from a simplistic standpoint. It is not just up-front costs. It is also the cash going into or coming out of the model through the life of the model; the discount factor, which I will get to in a minute; and then your up-front investment. There is another aspect, and I didn't want to turn this into a discussion of finance, but you also have to ascribe a terminal value because the cash flow doesn't just stop. So you have to have a way of accounting for the life cycle of the product, and you do that. So there are some other aspects to the model, but I didn't want to sort of complicate the presentation with those issues.

The up-front costs will depend on the nature of the product, whether in fact it can be derived from your existing fractionation of plasma, whether you have additional facilities that you need to put into place. In my example I made a very modest assumption in terms of the investment for capital because in many instances for fractionation we do take advantage of some costs on the basis of we have a facility in place, we are taking products already through that facility. One has to look at the chemical nature of the product and where it is being removed. You also have to look at I guess the fractionation scheme. No two plants are the same in terms of their fractionation schemes. You could impact the economies or in fact the reg status of another

product by having that to defractionate an additional product from the scheme. So those are all factors that one has to take into account.

I don’t think there is a simple answer, and the reason I focused on the investment for the clinical trial cost when I was asked the question was I was trying to put it into the context of this audience. The audience I think is not here to consider manufacturing capital investment. They are here to look at I think the registration and the clinical considerations, so that is why I framed the question that way. If I had a different audience I probably would have chosen another up-front cost to be concerned about.

So I don’t know if that is the answer to the question, but I think there are a number of areas that one could look at, and certainly you can leverage if you have already the product approved that you are manufacturing in another jurisdiction. It becomes a much more simple case to look at for registration in an additional jurisdiction, and it depends on the chemical nature of the entity.

The second question was in respect to -- can you remind me? I am sorry. My answer went on too long.

MR. EPSTEIN: To characterize the kinds of risks that you consider in the discount rate.

DR. WALTON: Yes. The discount rate was entirely from a -- I am talking about risk from a financial, and what

that is used for, it is actually a measure of the cost of capital. If we had to at a particular point of time either had to go out and borrow or raise money on the share market, which is essentially borrowing anyway, it is what the going rate is for that money, and the risk comes down to how much guarantee you can give to actually have a return. So it takes into account risk of success for the program going forward, if you fail and you don't achieve a return on that capital, so more higher -- our industry has a certain level of risk. We use numbers that are given to us by finance on the basis of how the market looks at investment out of our industry, and it really encompasses the entire risk of the project coming to financial fruition. It doesn't take into account other aspects of risk such as safety, et cetera, et cetera, that one may think of. It looks into entirely will this project succeed or fail, and if it does will it succeed and return the investment that we modeled up front.

DR. DASH: Can I make two other aspects? I think in a way to make it simple, you can change the cost of developing a product, a new protein out of plasma, by looking at it in two different ways. Once you have bought the plasma and you have used it to manufacture other products, that plasma that you have a valuable protein in potentially is not costing you any more. So you could say I could discount the cost of that plasma. So the first phase, if you like, of the

development of the plasma costs, and that could be zero if you wanted to. The second phase is the capital investment and the validation of the capital investment and any other facilities that may need to be validated or increased or expanded, and that is clearly one of the things that Paul talked about, and then there are the clinical trials which we have heard much about. So you could divide it into three things, but at the end of the day we generally want to make the new product make a contribution to the overheads, so therefore the plasma costs are not regarded generally as being zero.

MR. SANTAS*: Sam Santas* from the Alpha One Foundation. Two quick cautionary kind of tales for your comments. One is probably the reason that a lot of us have an emotional negative reaction to NPV calculations and things like that is the knowledge of some extremely successful products for rare diseases that failed their initial NPV calculations. Recombinant growth factor, things like that, and so I would like to know how you pick those out from the -- using calculations and things like that. Then the second is the one that I am most familiar with, and that is how Alpha One has sort of been hampered by its success in trying to what other rare diseases are doing. I mean, after all, the therapy, the initial therapy for Alpha One was approved by a mechanism that allowed for its marketing without really

any efficacy trials, and that was in the 1980s when there were only about 200 Alpha One patients identified. Now there are 20 times that number identified and in the past some shortages of drug, and we expect that there may be 20 to 50 times that number identified over the coming decades; and we are in a situation where patients and physicians believe their drug is extremely effective, and yet we can’t do placebo controlled trials because of that perceived effectiveness and we can’t do a comparative trial because the efficacy --- were never done. So I know that many of you would like to be in that position with your patient populations because the first drug -- you don’t even have that first drug, but I just would like your comments on how much you are looking into the future as you bring these drugs forward.

DR. WALTON: The first rule of any modeling is rubbish in, rubbish out, and these are models we are trying to make a predictive assessment over two decades or more in most instances. So to answer the first question, I don’t think any enterprise or any of the plasma therapeutics companies set out to come up with incorrect or false outcomes in their models. They do the best they can with their inputs, so given that, we seek -- in building these models we crank the numbers, but we seek input from our management and from skilled individuals in and outside of our organization

and we do the best we can. If we clearly get it wrong due to the fact that only one percent of the target population is being diagnosed today then that is on the basis of information that we knew at the time, but I think what we have to endeavor to do is to have the tightest and best assumptions. The rest of it, you know, running the model is pretty easy to do. The model depends on the inputs and assumptions, and that is the way to get quality conclusions. The second point I am not sure if I am --.

DR. DASH: I would just like to add the point that whether it is NPV or whatever, this particular hypothetical project that we are talking about is probably not the only project going on in the organization at that time; and so that has to be lined up against several other projects, and the NPV calculations might be done across the whole board in similar types of assumptions. So then you have some theoretical comparison and say, "Which are our priority ones?" Some of the priority ones in this day and age is ever enhancing the safety, the validation, and some aspects of prime clearance for instance, and those things obviously take a degree of priority. They all take revenue. They all take capital, and they are all vying for a similar pot of revenue capital; and each organization has a pot of whatever size, but it is the same size pot year on and year on if you like, and they have to fight for that prioritization.

MR. SKINNER: We will go back up to the back of the room.

DR. NUGENT: A good reason to sit in the back. Thank you. I am Diane Nugent of Region Nine Hemophilia Community. Great discussion so far. I would just like to simplify some of this by saying that as someone who cares for patients and is involved in getting products to patients it is fearful to hear the degree of financial commitment both by companies and stockholders that we are banking on to provide product for very few patients in this country. So part of the reason I am here and the little political box I am sitting on is how can we make this a reasonable risk for these companies without opening the Pandora's box of saying -- and I will use just to keep this politically correct metabolic disorders, where very, very rare diseases now have products available at great cost and great expense that are curing disease, but which now we as treaters realize are probably going to be very useful to a huge number of patients with vascular disease or undiagnosed adult metabolic disorders. As a company, that makes it more attractive to develop a product knowing that that audience is out there. So, Dr. Silverman, I am wondering how difficult or how does the FDA look at a product for rare disease that sort of in the back rooms you know is going to explode as an unindicated course. How can we make this cost-effective for these

companies, and I will take your response offline.

(Laughter.)

DR. NUGENT: No, no. I didn't mean offline here. I mean I am going to click off here.

DR. SILVERMAN: I guess I am not off the hook then.

(Laughter.)

DR. SILVERMAN: Well, obviously FDA must consider licensure. This has come up in other arenas as well as other members of this audience well know. We are allowed only to consider the indication that the company actually seeks. An off-label use, while in the background and while on our minds is something that, you know, we think about, but we are obligated to look at what is before us. You know, that is the short answer to it. You know, there are mechanisms by which FDA if, you know, something is used massive off label there are mechanisms where FDA can ask for, I think even require, clinical trials to support, but that would be once the product is already approved for its orphan indication.

DR. SILVERMAN: Dr. Hoots.

DR. HOOTS: A question for Dr. Dash. In one of your slides you showed the myriad of products that are available in Europe country by country, just alluded to them without specifically saying which was which. How does the interrelationship between say a country in Europe and the EMEA inform the dialog about harmonization? Like if Country

A produces an orphan product, a factor let's say that is rare, how do they decide first of all that they are going to go beyond the country's borders to the EMEA and how does that help us in the United States to the next phase of harmonizing to get that product into the United States? Is there something about that process that could teach us something about potentially about streamlining exportation outside of the EMEA?

DR. DASH: Well, I will try to answer some of that. Maybe some of my other colleagues could contribute. I think the decision really comes from the manufacturer initially. Does the manufacturer want for any reason or does not want for whatever reason to go outside the national boundaries with this particular product? Many of the products that I mentioned this morning are historical products; and they were, if you like, developed in the days when the member organizations were very much more national, and they were doing it under the auspices of the national government in order to try to help those patients in those territories. While they were done to the best standards, they might not necessarily, to quote what someone had before, had the BLA brought up to date necessarily. I don't whether any of us would like to contribute from ---.

MS. ROSSI: Hello. Françoise Rossi from LFB. There is one contradiction in the EMA drug registration, and

I know that that will be explained later on this morning. It is that whenever a product is available in one country it cannot get the orphan designation, the European orphan designation. So for all these products that you have seen, there is in no way in the same, very same clinical situations a clinical indication to get the orphan designation and of course not the registration.

MR. : I would like to come back to the Alpha One story because I think it represents an interesting conundrum. A couple of you in the audience may remember that I was on the external FDA committee that recommended the FDA approve that. As you say, that was in the late ‘80s, and it was based on what I guess is now outdated, incorrect information. The committee recommended at the time based on the its biochemical equivalence, and as you say with zero efficacy data, based on the concept that it would have taken enrollment of every patient in the United States who was known at that time to be studied for a large number of years to show efficacy; and clearly that was not practical. If, on the other hand, and the FDA went along with that, on the other hand if it was known at the time that there was perhaps 10 or 20 times the number of patients that we thought at that time existed, the committee might have recommended something else, the FDA might have thought of something else. It would have altered ENPV calculations in two ways. One is a bigger

market, but on the other hand if they had to do trials it would have greatly altered the NPV. So I think there is a very great conundrum in terms of a balance between the number of patients to be studied, what kind of trials need to be performed, and what the net result of that might be.

MR. SKINNER: Other questions? Dr. Casper.

DR. CASPER: Thank you. Carol Casper, Los Angeles. We seem to be talking a lot about numbers, and I think that that is where we really need to focus a lot, and I want to commend the World Federation and Flora Peyvandi in particular for gathering numbers on how many people with these rare disorders there are. Dr. Peyvandi did it in Iran, and we did have one of Dr. -- Mr. Mark Skinner's slides showing that there were so many rare disorders diagnosed in Italy, and I think that it is because they were looked for and well-registered in Italy. I want to comment that when you look you may find a lot more people than you think you have, and I see in one of these handouts about 10,000 patients in the United States perhaps. I couldn't get a real good number, Mr. Castaldo, for hereditary angioedema, but if you --

MR. CASTALDO: There is really no good epidemiological data. I prefer to use some data that I extrapolate from Italy, and that brings me to about one in 50,000 per population. So we roughly think that there are 8- to 10,000 patients in the United States is what we are

currently looking at.

DR. CASPER: And I think that when you -- you know, the experience of the World Federation often is when you look to a country which hasn’t had a lot of treatment and then you have treatment then you find a lot more patients, but that happened in the United States, too. When you suddenly have a lot more patients, for example, who are surviving to adulthood and so the number seems larger, and I would like to say that we say $15-million development cost for something that might be 10,000 patients. I tell you, I guess I am getting used to large numbers because $15-million in California would cover the average medical costs of 100 people with hemophilia for only one year, and I wondered as an idea are -- that the small business model was suggested, and I don’t know the details of that, but some governmental subsidy for development for something that would be used for 10,000 people doesn’t seem so bad to me when we are talking about $15-million compared to the treatment of hemophilia. So I mean I think that doesn’t -- I mean, it is a lot of money for an individual company. It is not a lot of money for government. Thanks.

MR. CASTALDO: If I could just make another little point, because that does get us into the realm of numbers, and I think it is very clear in speaking to folks at --- it seems very clear than once a therapy is identified there is a

steep upswing in the number of patients that get identified. But right now even in our disease for example, now we throw around cavalierly these numbers that are really unsubstantiated at this juncture. They are only extrapolations. You know, but for purposes of getting a clinical trial done let's all remember that these patients don't fit in neat clusters. They are geographically diverse, and many of them have yet to really be identified. We are toying with the notion of a registry and looking at an international program to do something of that sort, but at this juncture we have not identified a whole heck of a lot of patients, which really complicates the ability to get a clinical trial done even with a purportedly, you know, relatively medium orphan population. So I think that is really key when you are looking at these orphan diseases.

MR. SKINNER: And I should have made one comment when I had my slide up there, because I think Dr. Casper made a very good point that I didn't make. It is the countries that showed up on the slide, the 20-some countries that I showed, may not be intuitive of the countries where you would think the patients are, but they in fact are the countries, you know, like Italy and like the UK and the US where there has been an effort to identify and find the patients. In fact we don't know where all the patients are and, you know, the organizations are resource limited just like the

manufacturers, but with a consorted effort in fact the patients can be found, and some of the countries that are up there demonstrate that the numbers are far greater than what had been anticipated and they can further be developed in the other countries as well. So the global data collection is an important piece, and that is one of the pieces that the patient organizations spend a lot of time focusing on.

Dr. Weinstein. Oh, okay. So we have got time for one or two more questions, depending on how long the question and answer are. In the back.

MR. : Yes. --- from Amsterdam. As the current chairman of the Factor VIII/IX Subcommittee of the ISDH, I am particularly interested in this meeting, and I would like to congratulate the organizers of this. And from this morning's participation I particularly enjoyed the one by Dr. Walton because it so openly addressed the financial issues, and at the same time I feel a slight hint of disappointment about this because for instance in the case B on the rare disease the net present value is about $7-million negative, and that would be prohibitive. Actually I think $7-million is not so much money, and if -- well, if we compared it for instance for the smaller countries like the Netherlands we developed the factor IX product for hemophilia B for a patient population that is no more than hundreds. So that is really very close to the situation we are discussing,

and our business evaluation was like that case B. So minus $7-million, that doesn't mean that it is prohibitive because all manufacturers have a product portfolio that can afford some risk in -- not many, but a few of these products. So having said this, I would like to have some response from Dr. Walton and Dr. Dash if possible.

DR. WALTON: I guess that the first issue is that, I don't know the number, but we probably have 10 or a dozen situations where we have potentially rare diseases. So there is a compounding factor where you look at competing resources I guess is the first issue. The second issue is the model was a simulation. It wasn't an exact modeling of any case. So whether it is 7- or70- or 15-, it was an illustration of the fact that under the decision rule, and the decision rule is if you have a negative present net value you don't go forward with the project, under the decision rule that is the outcome. I tried, I obviously didn't try hard enough, but I tried to so indicate that this is only one tool that we use. We have a number of financial factors that we consider. Management is not just driven by NPV models, otherwise it would be pretty easy to manage a company. There are a lot of factors that we take into account, so don't be disappointed by my illustration. It was simply, you know, try to think of it as a textbook case of how you use an investment analysis tool, and I think that there are opportunities open to

consider different situations. At the end of the day unfortunately we do operate in a capitalist system, and we require capital to run our business; and there are fine organization whose value-added function is social programs, and we would look to those to work with us in a coordinated manor to try and solve some of these problems.

DR. DASH: I would just add and perhaps reiterate what I said just now. If you were to take all those cases and they were different products competing at the same moment in time and you only had a limited resource, where would you put your money? You certainly wouldn’t put it on that one perhaps. You would put it on one of the other ones perhaps giving a positive return, and that is I think is the value of that together with the other scenarios. It is not the absolute number, but there are other competing resources required.

DR. PEYVANDI: There is one point we have to be careful on the distribution on the model that we are developing on rare bleeding disorder because the difference with hemophilia, there are some types of rare disorders like factor XI --- and factor VII there is no comparison with the severity of the patient and the type of bleeding. Because what we are going to see I believe in the distribution of the number of the patients affected by rare bleeding disorders who require treatment, the people less than 10 percent I

believe. But we are not sure in factor IX deficiency in ---, so there are some variant I think and this model has to be really ---.

MR. SKINNER: Thank you. I would like to thank the panelists, and this has been a fascination discussion for me. The insights into the business developments of the companies and all present a lot of challenges quite clearly for us. I think we have learned a few things, a few insights that maybe help us see some opportunities as well. So with that we will close the session and I turn it back over to Mark. Thank you.

(Applause.)

DR. WEINSTEIN: Thank you very much. Thank you, panelists, for participating. I would know like to turn the position of moderator over to Jonathan Goldsmith. Jonathan is the new Deputy Director in the Office of Blood Research and Review, and he will moderate this session on current opportunities.

Current Opportunities

Jonathan Goldsmith, MD, Session Chair

DR. GOLDSMITH: Thanks very much, Mark. I want to thank you and our fellow colleagues who have put together this meeting. It has clearly attracted a lot of interest from people from all the various constituencies. This is a very knowledgeable and diverse group, and I think that we are

fortunate to have them gathered here today.

This next session is entitled "Current Opportunities" and it is the current opportunities to move the rare plasma protein products closer to the market or maybe even to the market perhaps at the end of the day. Dr. Seitz from the EMEA will give the European perspectives on this; Dr. Jain is going to talk about US FDA and some trial designs that have actually been used for these disorders; followed by either Dr. Lachenbruch or Dr. Ng or maybe both will talk about some statistical considerations; and finally Dr. McCormack from Orphan Products, Orphan Drug Products, will talk to us about some incentives that office has to offer in bringing some of these products forward. Now Dr. Seitz is here, so he should take the podium.

European Medicines Agency (EMEA) Perspective on Licensure of Biological Therapeutics for Very Small Patient Populations with Rare Plasma Protein Disorders

Rainer Seitz, MD

DR. SEITZ: Yes. Thank you. Oh, God, the computer is in use and has been locked. In the meantime, I have the opportunity to thank the organizers, particularly Mark, very much for inviting me. We appreciate very much that you are inviting regulators from all Europe to discuss with us, and I hope I can present you something new about Europe.

First of all until the slides come up I can say a

few words maybe about the EMEA. Actually I am not working for the EMEA directly. I am working for the --- Institute, which is the German licensing agency for blood products. The EMEA was founded in 1993 and is the European medicines agency that provides so to say the platform for the European procedures and the Secretariat, and the organizational background most importantly the EMEA looks for the time lines of procedures to keep all the assessors working. But the actual scientific assessment is still done on the basis of subsidiarity by the national authorities of the member states, and one of these authorities is the --- Institute in Germany.

(Slide.)

Okay. The first slide I wanted to show to you is already dispensable because you have seen that already. Here we are. Okay. Thank you. So the first slide I wanted to show is already dispensable. You have seen this. We have in Europe a number of products on the market, but in most cases only in certain member states because these are quite old licenses. But also we have centralized license for this product and I will come back to that, and of course we have a list of products that we would like to have and still do not have. This could be expanded of course, and certainly as a basic statement the European Union is interested to get more products for rare indications.

(Slide.)

Of course Europe has also orphan drug regulation for giving incentives for that. I think I do not have to go in detail through all of this. Fee reductions, free protocol assistance, I think the most important is the market exclusivity for 10 years -- and I am afraid the pointer is exhausted. No.

(Slide.)

To get these incentives you need to get a designation as an orphan drug. The orphan drug must be intended for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the community. So to say orphan drugs do not really have to have very rare disease. For instance, also hemophilia would fit this definition. The second condition, it was already pointed out by Françoise Rossi. There exists no satisfactory method within the community, and even if in only one member state there is this a drug then this would make the designation as orphan drug more difficult. It is not impossible if you can show that your new product is better and brings about really a benefit above the existing product. Then you can still get the designation as an orphan drug.

(Slide.)

Okay. It can also be removed from the register. I think I do not have to discuss this in detail.

(Slide.)

Coming to the orphan designation for plasma-derived medicinal products, and as Françoise already pointed out, in may cases the products which are applying for orphan drug are not the first product of this kind. In most cases we have already some product on the market, and this is a little bit let’s say disappointing to the Commission because the spirit of this orphan drug regulation was really to get very new products for diseases not yet treated, but most of the companies applying for orphan drugs we are --- to have some more or less modified products and there are some arguments brought up for the designation. A very important argument is the increased supply. So even if you have a product in the member state and we have -- currently we have an example for that, and you can say, okay, this product in the member state is not enough to supply all Europe and we can provide a better supply it might be an argument, for instance in the case of factor XIII, also a more convenient route of administration. But the claim which is most often made for orphan drug designation, that it is an improvement in safety to transmissible agents is in most phases not accepted.

(Slide.)

Okay. This is the orphan drug regulation, and how about the products we are talking about here? There are some specific aspects of these products. We are not talking about

new chemical entities, new chemical substances of unknown characteristics. We are talking about plasma proteins, and in many cases the function of the lacking protein and the symptoms of the deficiency are very well established. So in those cases the clinical profile of fracture concentrate would be in principle predictable. For instance, we know that factor VIII will correct the coagulation defect in hemophilia and will produce hemostasis. So we do not need really randomized pre-licensing studies to show that. However, specific therapeutic products have to be evaluated in order to confirm they are efficacious and to assess potential adverse events such as immunogenicity, and this is of course not so easy. Immunogenicity may particularly be an issue in case of recombinant ---. However, the problem with these rare diseases is that we do not have enough patients available to perform statistically meaningful pre-licensing studies. Particularly that is very important in related undesired effects. I think that the problem is not so much with efficacy. The problem is to evaluate risks of these products, so we are in a dilemma.

(Slide.)

What we from the European Union can show you, we have certain regulatory mechanisms to license with limited clinical data, and this is of course a delicate thing because we acknowledge and we take into account that in some cases

you do not have the possibility to really perform convincing studies.

We have two mechanisms. The first on is called exceptional circumstances. This applicable if the indications are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. That means if the condition is so rare that they do not really -- you cannot be expected to have enough patients a meaningful study. There are examples. We have licensed the BeneFIX, the recombinant factor IX in this way and also protein C. I will come back to that.

However, of course there is a however, these marketing authorizations, this type of marketing authorization is usually combined with certain specific obligations which may include competition of an identified program of studies and notably also post-marketing evidence. About the post-marketing issues I will talk tomorrow.

(Slide.)

So the second regulatory mechanism for rare products is the conditional authorizations. This is applied when a drug is very -- to get this drug on the market is considered a very urgent thing and it is very desirable to have it very fast on the market, and so this authorization would be granted knowing that part of the evidence will be -- will follow after the authorization. So this is in cases

where you can expect that you have one day a complete dossier, but your are licensed already in an early phase before everything is complete because of an urgency, urgent need for this product. However, for products for rare plasma protein disorders it is more likely to licensed under the first mechanism I showed you, the exceptional circumstances.

(Slide.)

I would like to show you this on an example, a case study, the plasm-derived protein C, Ceprotin. This is a plasma-derived protein C concentrate and it was licensed under this exceptional circumstances by the centralized procedure. In this presentation of course I will not go into very much detail about the dossier and about the assessment by the EMEA. However, for centralized procedures we have in Europe a very nice thing, the so-called European Public Assessment Reports, the EPARs. And this is I think quite a meaningful report, and if you are interested in more details you can have this report from the website of the EMEA and hae more information about that. But as I saw also the marketing authorization --- provide further presentation during this meeting I think tomorrow on Ceprotin.

(Slide.)

So about protein C? Protein C is protein synthesized in the liver. It is activated by thrombin after binding to thrombomodulin. Certainly you know all that, and

the important thing is that protein C comprises a natural mechanism to control to coagulation system and to prevent excessive clotting which is important. Protein C deficiency is known to lead to increased coagulation activation and ultimately intravascular clot formation with thrombosis.

(Slide.)

A severe protein C deficiency is a rare thing. Homozygous protein deficiency are really only --- cases. Heterozygous is a little bit more frequent, and at least the clinically overt cases, the really symptomatic cases of lowered protein C level without symptoms, without obvious symptoms is more frequent, but the clinical relevant rare deficiency is a rare thing.

(Slide.)

There are two clinical features of protein C deficiency which are really severe and really dangerous. One is skin necrosis when oral anticoagulant therapy is started. There is a faster drop of protein C then after coagulation proteins. This is one of the explanations for this phenomenon, but it is certainly not the whole truth. I will come back to that. The second very important and very severe manifestation is purpura fulminans in homozygous newborns which is a highly life-threatening state.

(Slide.)

I will just show you two pictures. This is from my

previous life before I joined ---. I was working in the University Hospital in Georgia. These were two cases of skin necrosis and I am not sure whether you can see in this projection. There you see the big necrosis, the black, and around this necrosis you see a red zone which is clearly a kind of inflamation. So protein C has certainly also some connection to inflammatory reactions, and then around that you see a hemorrhagic zone with also petechial parts.

(Slide.)

When this product was developed by the applicant it was first not intended to develop it commercially, but the company had a company of preclinical testing and of course a quality program to qualify the product. However, when physicians became aware that the company would develop protein C, there was a lot of request for having this product for compassionate use. This compassionate use continued over a number of years and included very severely ill patients with quite interesting clinical features, and then at the end after getting some pressure from the physicians the applicant decided finally to develop the product for congenital deficiency. What I call compassionate use here was really more or less compassion, not so much a regulated thing.

(Slide.)

We have now as a new feature in the European legislation something about compassionate use. This a new

thing. First of all, it is an issue of the member states. The member states have to declare that they want to have a drug for compassionate use. The drug may be made available for compassionate reasons if there is of course a group of patients who would need it with life-threatening and severe diseases, and, which is important, the medical product must either be the subject of an application for marketing authorization or which must be undergoing clinical trials. So as I told you before, if the company has something interesting and then gives it away for compassionate use this is no more possible with the new European legislation. In this case you would at least have to have application for a clinical trial, and the GCP directive would be another story. Maybe next year I will tell you about that.

(Slide.)

As I already said, the protein C was licensed with limited clinical data. The applicant provide a dossier with full safety and preclinical evaluation, and this is of course very important. There is no compromise with the quality of the product and the preclinical aspect and particularly the virus safety of factor product. However the available clinical information was not at all what you would like to see for a new chemical entity. I do not want to go into details as I already said. If you are interested in details you should compare the EPAR about this product.

(Slide.)

Then the protein C was licensed and the indication accepted in the marketing authorization was the substitution in purpura fulminans and coumarin-induced skin necrosis in patients with congenital protein C deficiency. This is more or the less the core of the indication. However, also in certain risk situations protein C concentrate is indicated.

(Slide.)

So to summarize this again, what I have told you about such a product in this case. The first thing is the identification of a protein deficiency and the specific and severe clinical consequences, then preparation at least was developed under R&D aspects. You should have something in your hand before you think of further clinical development, and in this case it was very important and I think it will be also important in other rare diseases. A clear demand expressed by physicians and/or patients, and then which is central for us at least at the EMEA, you need an adequate quality and pre-clinical qualification of the preparation. There may be some compassionate use and pilot study which contribute to the clinical data, but in the end we have now mechanisms in Europe for licensing with limited clinical data and, as will tell you also tomorrow, there is a strong accent on the post-licensure program.

(Slide.)

Just to mention it, in Europe we have a new guideline, a draft guideline released for six-months consultation, a guideline for clinical trials in small populations. Maybe this also interesting reading for you. I do not go into to the details because it is not yet in operation, but you have still time to comment. If you are interested you can find it on the website of the EMEA.

(Slide.)

Now I would like to touch on another point which was already mentioned in this meeting. How about acquired disease? It was already said that the company might try to get a license for an orphan indication and then come to the real big business to acquired deficiency. In the case of protein C, this is of course a very important thing. These are pictures of a patient with sepsis, and to see it is more or less very similar to what we have seen about the coumarin necrosis. You have again here necrotic areas in the skin and adjacent to that hemorrhagic. So again in very near neighborhood necrosis and bleeding, and here you have also necrosis of the fingers in this case. This is seen very often in meningococcal septicemia, but it is not restricted to meningococcal. You can see it also in other bacterial, severe bacterial, infections.

(Slide.)

So while congenital protein C deficiency is rare,

an acquired deficiency occurs much more frequently, and of course it is intriguing to try these preparations also in these cases and there are in fact intriguing clinical data about that. However, since the efficacy safety profile of this product has not been fully established yet, its use is deemed relatively safe and effective only in the severe clinical conditions for which it is indicated. That is more of less the statement of the European regulators, but of course you see that there is some problem and there is not really a golden way to avoid it if somebody wants to do things like that. Of course there is an overlap with licensed recombinant activated protein C.

(Slide.)

So at the end I would like to tell you a little bit about a specific group at the EMEA. I think the discussion before there was the question of how about guidelines, how about criteria for clinical studies, what is the validated endpoint, surrogate endpoint, and so on. In Europe we have a working group on that, the so-called Blood Product Working Party. I have the pleasure and the honor to be a member of this group. We work on all efficacy and safety aspects related to blood products. We are producing notes for guidance, but also core SPCs that will be also a very important topic for discussions, and give advice to CHMP, but also scientific advice to applicants. For more information

and documents of the guidelines again you can visit our website, the EMEA website.

(Slide.)

Just to point it out, the EMEA approach to clinical evaluation of products for rare protein deficiencies is a little bit different to what we have heard this morning. The requirements are not driven by statistic criteria. We say that very clearly and we admit that this is really a decision in Europe which has been taken. Of course we are on the safe side if you have good and valid statistical data, and of course the regulators take some risk if we say, okay, we are ready to think about licensing also without convincing statistics. This is of course only in cases where we have a limited number of available patients. The pharmacokinetic profile of the product has to be evaluated and efficacy has to be demonstrated, however again not in big randomized --- studies. There are specific requirements for specific products. For instance, we have a guideline about factor XIII where we say clearly what we would like to see.

It is understood that pre-licensing clinical studies alone will not provide full assurance of safety, and I think that is fact and I think it will be difficult anyway to have for biological substances really an absolutely assurance of safety before you can license. But however a very important thing is if we had a problems with blood

products at least in the past decade it was mostly about the pathogen safety, about the virus transmission; and I say very clearly for us in our view the virus safety, the pathogen safety is no more a subject of clinical studies. This has to be shown by qualification of your manufacture of your source materials by testing and so on, by validation studies, but no more by clinical studies. Rare and/or delayed adverse effects should be addressed of course in pre-clinical studies, but notably by post-marketing studies. If you have only a limited number of patients it would be very difficult to find out every risk before licensing, and we think, and I think we come back tomorrow also to this point, that registries of patients with rare protein deficiencies would be very desirable and helpful with this respect.

(Slide.)

At the end, I would like to give you two examples of the work of this Blood Product Working Group. This one is from the factor VIII guideline which can be found also on the EMEA website. These say we want to see at least 50 previously treated patients. If you are a statistician you would say, "That is ridiculous. It is not enough to find anything. You have to have to have at least 80 or 90 patients." On the other hand, Clive Dash would say, "Oh, 50 is horrible much for small countries with limited resources," as we have heard. So this 50 I say clearly was a compromise,

and we are confident that with 50 patients we would at least find a signal if there is something wrong with the product. However, clearly not clear-cut data before licensing.

(Slide.)

The other example I would like to make is the evaluation for antithrombin products. In these notes for guidance we have taken into account the rarity of the congenital disease with criteria adjusted to that; but we also take note of the indication for acquired deficiency, and you know that antithrombin was really evaluated for the efficacy in acquired deficiency, particularly sepsis. There was the Kybersept trial published in JAMA. Unfortunately this trial failed to show efficacy with regard to the predefined primary endpoint.

(Slide.)

So to summarize the talk, it is an objective of the EC to encourage development of medicines for rare disorders, e.g., by means of the orphan drug legislation. In rare protein disorders, not enough patients are available to perform statistically-meaningful pre-licensing studies. However, if protein function and symptoms of deficiency are well established, the clinical profile to some extent would be in principle predictable. There are regulatory mechanisms in the EC to enable marketing authorization with limited clinical data. However, that means -- I have to say it very

clearly -- that means that licensing is not difficult for us because we have more or less case-by-case analysis. We have to assess each case very, very carefully whether the clinical data are sufficient or not, and of course I have to mention that the EMEA and the Blood Product Working Group would be happy to provide specific guidance if needed. Thank you very much.

(Applause.)

DR. GOLDSMITH: I think we can maybe take one or two questions because we have a 12:00 lunch break which has already passed. So I see three questions in a line here, so --- first.

MR. : A very interesting talk with a lot of information. I found the core specification concept was very interesting. Now for the rare disease --- product that you have, you probably don’t have that much existing license product for that rare disease. Where does the data come from to support your core specification concept, or that is not applicable to the rare disease?

DR. SEITZ: Which --- concept do you mean?

MR. : Well, you mentioned that you are working on the core specification.

DR. SEITZ: The core SPC.

MR. : Right.

DR. SEITZ: The core SPC, the core summary of

product characteristics, that is a topic of the group, but I did not really talk about that. This is for instance for immunoglobulin, for albumin. You have the core SPC which covers more or the less the whole group of immunoglobulins or albumin, but this is not a think for rare protein diseases.

MR. : I see. Okay.

DR. SEITZ: We do not have to. This is really for well-established products. I have to say, okay, this is a class of product and we know what they are doing, and we give guidance for the SPC, general guidance for SPC.

MR. : Okay. Another very quick question is you mentioned no compromise on the CMC for the rare -- for the orphan drug. Now what kind of data that you would like to obtain to get to support -- let’s say to support specification and also to support the process validation? Is there any reduced requirement on the process validation for the product ---?

DR. SEITZ: No. In principal there is no certification. We would for instance protein C, we would assess protein C like we would assess factor VIII or factor IX concentrate from the standpoint of quality, qualification of source materials, validation of production and so on. There is no difference. The difference is really on the side of clinical data.

DR. GOLDSMITH: Diane in the back.

DR. NUGENT: One of our challenge here beside the microphone is, you know, with rare diseases it does take so long to do the clinical trial and capture all the side effects. So post-licensure followup phase IV trials are really critical for this population. But it is still here sort of a voluntary participation. Do you in your system have a less-voluntary way to capture that data?

DR. SEITZ: A less-voluntary way. No, we have no legislation obliging patients to participate in clinical studies, no. But of course you touch a very important point. Also if we say, okay, we are ready to license with limited data and we want to see first licensing data it is of course crucial that everyone contributes to that and contributions of the patients and the treating doctor is crucial in this context. A bit of a problem is with these licensing with applications that the company will say, "Oh, yes. Of course we will do anything you want," and if they have their license and are 10 meters away you will never get them; and that is really problem and if you try to catch them they will say, "Oh, the doctors do not cooperate," or "The patients escaped. They do not want to." You know, that is really a problem of how to enforce that.

DR. GOLDSMITH: Okay, and then last Donna.

DR. DiMICHELE: Actually thanks again for this presentation. I agree with Diane about the post-marketing

surveillance because you do put a tremendous emphasis on it in your licensing procedures, and yet it is not enforceable. So I think that may be a weakness of the European system and certainly something that we can't rely on in this country in terms of, you know, looking at data that exists, you know, for products that are pre-licensed in Europe before they are licensed in the US, so it is a bit of a liability. But my second question is the issue of the method by which most of the products for rare bleeding disorders would be licensed in Europe. You had said that the exceptional product pathway is generally what is used, but do you also use the new pathway, the compassionate new, in parallel to gather data for licensure of your products? I didn't understand which mechanism was being used right now.

DR. SEITZ: No. Compassion use is something else. This may happen before license is granted and may be helpful for data. But there are two pathways for licensing with limited data. One is exceptional. That means it is so rare that you cannot expect that you get comprehensive data. For instance, if you have 20 patients in the world you will not get a big trial. That is first of all. The second way is licensing under conditions, conditional licensing. That means that you get the license very early where the studies are not ready, but you still expect that they will be ready someday. So in cases where the deficiency is not so rare.

So for instance they have -- how should you say? You give a bit of a credit to the company. Okay? You get the license but you promise to go on with your studies to have a complete dossier one day.

DR. DiMICHELE: So you are not using compassionate use data to grant to licenses for products with rare disorders in Europe then. Is that what I am understanding?

DR. SEITZ: Yes, we do if we have good data from compassionate use. That was in the example of protein C, and the good thing with protein C was it was available in principal for years before really an application for authorization was submitted. In these years where everybody knew the company was concentrating on protein C there was a lot of compassionate use, and these data which were generated in this phase were of course used also during the licensing process.

DR. DiMICHELE: And were they used exclusively? That is the question. Was compassionate data used exclusively to grant licensure, or did there need to be studies in addition to that?

DR. SEITZ: No, I tried to explain. In those days there was not yet legislation about compassionate use. It was really just compassion, that everybody knew the company had a protein C and I have here a patient that might benefit. That’s it. So protein C was tried in those days not only for

the congenital disease, for the rare disorders, but also for acquired disease, for meningococcal sepsis and so on. But of course during this phase there was some information derived about the congenital disease which was useful in the process of licensing, but not in the sense of structured studies or something like that. It is just additional information which was interesting.

DR. GOLDSMITH: Okay. I think we will call this a close for the morning. I want to thank everyone for their good questions and good attention. We were to resume at 1:00. I think we will aim for 1:00 and see what kind of fallout we have around 1:00. Okay. Thank you all.

(Whereupon, a luncheon recess was taken.)

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

DR. GOLDSMITH: And now we go back to some really good mental exercise. Dr. Jain from FDA Office of Blood, Division of Hematology. Okay. We are back in session, guys. Back in session. Dr. Jain is going to talk about the FDA perspective on current clinical trial designs reviewed by the Office of Blood for very small populations with rare plasma protein disorders. Dr. Jain has dealt with these for quite a while and she will tell you some practical things about what has happened.

FDA Perspective: Current Trial Designs Reviewed by OBRR for Very Small Populations with Rare Plasma Protein Disorders

Nisha Jain, MD

MS. JAIN: Good afternoon. I am Nisha Jain and I am the medical reviewer in the Division of Hematology Clinical Review Branch, and today my topic for presentation here is clinical trials designed for products intended for very small populations. It is not exactly and FDA perspective, but some part of it is FDA and some part of it will be my perspective; and as you all can know it is a very difficult topic and this is difficult because there is no one trial which I can talk about which would cover one whole paradigm or perspective of diseases which we talked about this morning during our morning’s presentation. I guess part

of the responsibility goes to Mark, and I guess when he was looking for somebody to give a difficult topic he found me and gave me this topic to talk about. But I will try to see if we can generalize some aspects of the clinical trial designs for some diseases.

(Slide.)

So the overview of my talk today will be I will start with the definition, go on to introducing some of the rare diseases, the products which are licensed in the US for the very small patient population, the trial design recommendations for plasma-derived product and recombinant or other novel products, the various procedures present for approval, and the FDA incentives.

(Slide.)

Section 526(a)(2) of the FDA Act defines rare disease or condition for purposes of orphan drugs as any disease or condition which affects less than 200,000 persons in US, or affects more than 200,000 in US and for which there is no reasonable expectation that cost of developing and making it available in US for such disease or condition will be recovered from sales in the US of such drug. This will be covered in detail by Dr. McCormack later on during this afternoon.

(Slide.)

But the scope of this workshop is actually not

limited to those orphan drugs which are basically intended for less than 200,000 patient population, but limited to only the plasma protein disorders -- we are not going to talk about the metabolic disorders -- that affects very small population, i.e., affecting tens or a few hundreds. For example, taking the example of congenital factor XIII deficiency; the prevalence of this is one in 1,000,000, the pattern of inheritance, autosomal recessive; and as for the registry there have been only 200 patients described worldwide. The homozygotes presence with life-long bleeding requiring prophylaxis every two to three weeks because of the prolonged half-life of factor XIII.

(Slide.)

The second example would be congenital ATIII. Now there is a difference between the first and the second example here. Here the prevalence here is one in 2,000 to 5,000. The pattern of inheritance is autosomal dominant. These patients, they will otherwise lead a normal life. That means they do not require ATIII replacement therapy, but they are at risk of thromboembolism only during surgery or pregnancy, thereby limiting the sample size. The prevalence may be very high, but the patients intended for treatment or requiring intervention leads to -- limits the sample size. The risk of thromboembolism in these patients can be as high as 50 to 60 percent. So for purposes, you know, for my

purposes, I would define these diseases as super-rare conditions or diseases.

(Slide.)

What are the FDA challenges? We have heard the challenges since the morning for the industry perspective. Dr. Silverman gave an overview of the FDA requirements for licensure of products, but just to briefly put in the FDA challenges is quantity of evidence necessary to support effectiveness and safety is very limited because of the limited sample size. The estimates of safety and efficacy may also have wide variability because of the wide variations in the disease spectrum. Adequate and well-controlled, which actually is the definition, is one of the definitions for the evidence to support effectiveness, is very difficult in this patient population again because of the limited sample size. The appropriateness of historical controls also has its limitations. The natural history of the disease if available, i.e., if patients with that disease got no intervention as opposed to patients getting interventions and showing a difference between the two could serve as a control, too. The use of surrogate endpoints leads to reliance on post-marketing data collection which again has its own limitations. There is no provision in US for temporary license like there is in Europe, and Dr. Seitz had given an example in the morning. Sometimes the real need of

the product is actually not established, i.e., if FFP is used for the treatment of some of the diseases then the real use of developing a new product is not established.

(Slide.)

The industry issues. We have heard this morning from Paul Walton about the cost of development because of the limited market and not being profitable. There is not much incentive for the industry to develop such a product except for a larger off-label market where the product has not been studied. That could be one of the incentives, and of course least but not the most is the regulatory challenges which we of course, you know, do not impose most of the time.

(Slide.)

Coming to the products which are currently licensed in the US, the plasma-derived products, and I am going to give you one example of a plasma-derived product licensed in the US and the clinical trials required for -- which supported the licensure of that product. Talking about Thrombate III, Bayer’s product, this is an antithrombin III, plasma-derived, licensed in 1991. The indication for use of this product is for treatment of patients with hereditary ATIII deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism. Studies required or the studies conducted for licensure, the preclinical study for preclinical they had very well in vitro

characterization by physico-chemical properties and biological activities. Animal studies to study both acute and repeat dose toxicologies were done.

(Slide.)

Clinical studies consisted of two main studies. One was a PK study and the other one was a safety and efficacy study. The PK study was done in 10 asymptomatic patients infused with 100 IU/kg ATIII. The mean in vivo recovery was analyzed both by the immunological assay and the functional assay, and even the half life was done by both of the assays. As you can see, there was a very correlation not very far apart between the immunologic and functional assay. Both the in vivo recovery and the half life actually was equal to what was present in the literature.

(Slide.)

Okay. The safety for efficacy, an open label, single arm study was done. This was done in 13 patients who had a previous history of thromboembolism including pulmonary embolism; and as I mentioned earlier these patients who had previous history of thromboembolism are at risk of developing a second thromboembolism, and the risk can then be as high as 50 to 60 percent in these patients. These 13 patients included 11 surgeries and five deliveries. Heparin was used in three of the surgical patients and five out of the five deliveries. The dose was calculated to maintain the plasma

levels at 70 to 120 percent, and the duration of treatment in the study ranged from eight to 23 days. The outcome of this study was no patient enrolled in the study, that all 13 patients, did not develop thrombosis. This --- was approved in 1999, and it was actually compared to what would have happened if they were not given the intervention. That is 50 to 60 percent or as high as 70 percent would have developed thromboembolism showing that no patient developed with the use of this product. We thought that it was substantial evidence of effectiveness and this product was hence licensed.

(Slide.)

The safety of this during the clinical trial was mainly related to infusional toxicity and viral transmissions because in 1991 that was still a concern and there was no viral transmission over a period, 13-month followup period.

(Slide.)

The second product which I am going to talk about today is the Humate P. This is different because the population is not as rare as the congenital ATIII population, but it had a different aspect for licensure. Humate P is antihemophilic factor/Von Willebrand factor complex factor. This was originally licensed in 1986 for treatment and prevention of spontaneous and traumatic bleeding in hemophilia A. In 1999, it was licensed for severe von

Willebrand disease or mild and moderate where desmopressin is not adequate.

(Slide.)

The licensure of new indication based on the following studies was basically at the time of submission of the biological licensing -- I am sorry, something is -- at the time of submission of biological license or the interim report of the prospective PK study in asymptomatic patients with Von WIllebrand disease was submitted, types I, II, and III. Efficacy and safety was basically dependent on the retrospective review of data from 97 Canadian Von Willebrand patients who were given the drug under the Canadian emergency drug release program. The efficacy rating was excellent in 100 percent in type I, II-A and B and 95 percent in type III patients. Adequate dosing information could be gathered from this retrospective review, and the data gathered was also done under a systematic format. The post-marketing commitment at that time during the licensure of this was to evaluate the product for elective surgical use in Von Willebrand patients. So I brought this example up to shoe the flexibility of FDA, that if a product shows evidence of effectiveness, you know, we are willing to look at the data. You know, even if it is a very retrospective data.

(Slide.)

For recombinant products there are none licensed

for the very, very small patient population at the present time in the US.

(Slide.)

Now coming to clinical trial design, which I think is the most difficult part of this talk, I just want to first let everyone know that clinical trial design will be actually done on a case-by-case basis. But I have a general overview in my slides here because different products require different development programs, different diseases need different types of evaluation, and there is no statutory provision for generic biologics.

(Slide.)

So coming to a new product for this very, very small patient population, what would be required generally for licensure of a product? Starting from preclinical studies, it needs to be well-characterized in vitro including physical chemical properties and biological activities. Animal studies if it is a plasma-derived product it has limited or relevant toxicological studies. I would say limited because of the plasma protein, and sometimes if a relevant model is available perhaps a dose range and efficacy study if a previous clinical effect of that product has not been recognized.

(Slide.)

For clinical study, a PK/PD study in mostly

asymptomatic conditions evaluating standard PK parameters. A sample size usually will be variable because of the limitations in the sample size, but usually it is 12 to 15, and that may generally sometimes be all the patients diagnosed with that disease recognized. Sometimes a dose ranging study may be required. An efficacy and safety study in the appropriate patient population, the efficacy can be evaluated by either clinical endpoints or surrogate markers, and if the surrogate marker is not validated it needs to be validated in post-marketing commitment. The control study is again very difficult, but at times historical controls may be used to evaluate efficacy.

(Slide.)

Safety because of the limited sample size will be very limited pre-licensure. Most of the immunogenecity if it is a problem is usually not adequate pre-licensure, so most of the safety information would have to be gathered post-marketing. Statistical consideration, and Dr. Lachenbruch is going to go into details about statistical consideration for a clinical trial design for these very rare disease disorders, but just to briefly mention that there could be some more efficient use of design. Maybe consider one-sided confidence instead of two-sided, and maybe with a reduced power. Most of these cases will be heavily dependent on post-licensure or post-marketing evaluation for further

safety and efficacy because the pre-licensure data is going to be limited.

(Slide.)

This is for a product for which there is a product licensed for the same indication is available. So if a second manufacturer wants to come in for similar indication or same indication, then most of these trials for licensure would be comparative crossover PK with the licensed product. We would generally accept some efficacy or safety data pre-licensure, but not all of it, and heavily dependent on post-marketing efficacy and safety data.

(Slide.)

Now the products which have been licensed elsewhere, like for example in Europe, the question comes would we accept that data for licensing in the US. Well, foreign data is acceptable if it meets the requirement of 21 CFR 312.120 which states FDA accepts such studies provided they are well-designed, well-conducted, performed by qualified investigators and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United States and/or marketing approval. Marketing approval for a new drug based solely on foreign clinical data is further governed by 312.106.

(Slide.)

Which states that as a sole basis for marketing approval an application based solely on foreign clinical data meeting US criteria for marketing approval may be approved if the foreign data are applicable to the US population and the US medical practice, the studies have been performed by clinical investigators of recognized clinical competence, and the data may be considered valid without the need for an onsite inspection by FDA or it FDA considers such an inspection to be necessary.

(Slide.)

Moving on to the clinical trial requirements for recombinant or novel entity, again the product will need to be studied in preclinical situations leading to in vitro characterization, again related to the physical chemical properties and biological activities, and well-defined animal studies like the plasma-derived products. The recombinant products will have to be studied in animal models for toxicology studies, both repeat and single does and in appropriate models, if available efficacy and dose ranging.

(Slide.)

PK safety and safety, most of the times we will recommend comparative PK with the plasma-derived product if available. If the PK is comparable to the plasma-derived product, the same dosing schedule may be applicable for future studies. But if the PK is not comparable to the

plasma-derived product, then there may have to be a dose ranging study to establish the appropriate dose to maintain appropriate plasma levels and to compare the assays to detect the biologic activities.

(Slide.)

Efficacy study again like the plasma-derived products may be based on either clinical endpoints or surrogate markers. Again, historical controls or active control with a plasma-derived product can sometimes be used, but again there is limitation of sample size here. So, again, Dr. Lachenbruch is going to talk about how effective a control, what statistical plan could be used to establish to show the control equivalency or inferiority or superiority or whatever the statistical consideration is. The safety immunogenicity have to be actually well-defined and the assay has to be well-developed to detect neutralizing antibodies and general safety data has to be collected. Again, the reliance will be on post-marketing commitment to evaluate the safety and efficacy of this product.

(Slide.)

Now for products which are licensed for one indication but can be used for another indication, PK in the relevant population for the relevant indication has to be performed. Efficacy in the relevant population has to be shown. The only place where all the safety information can

be gathered post-licensure is with regards to safety, but that is only if there is no reason to believe that safety will be different in this new patient population compared to what has originally been indicated for the original indication, and, again, post-marketing commitments.

(Slide.)

So what are FDA incentives? Orphan drug status and grant. Again, Dr. McCormack is going to talk in detail about this this afternoon later on. Faster methods of approval once the chemical trials have been completed called accelerated approval, which are basically approval based on surrogate endpoints, but with the provision of validating the surrogate endpoints as post-marketing commitments. Priority review usually, you know, is a six-month review. All the guidance documents relative to this are available on FDA's web page.

(Slide.)

So in conclusion, FDA does understand the need for development of such products and we are willing to work with the manufacturers and physicians on any ideas of how to bring these products to the market ---. Thank you.

(Applause.)

DR. GOLDSMITH: I think we can entertain maybe one or two questions if there are some for Dr. Jain while she is still close to the hot seat. Okay. If not, we can do this

during the discussion period. Oh, there is one. I just can’t see the hand. Oh, please.

DR. GELMONT: David Gelmont. Dr. Jain, why the FDA is requiring or suggesting historical control? We know how much difficulties it is with assessing previous practice as is presented in the literature. Many investigators don’t present or don’t publish that data. The quality of the information is very poor, and it is many time the time between the published data and the current time of the study is so far and very difficult to establish any kind of relevance of historical control.

DR. JAIN: Actually I wasn’t recommending. I was saying there are limitations to historical controls. Adequate and well-controlled studies of this patient population are very difficult related to the historical control which has its own limitations, you know. You very well know what are the limitations of this. But I think you know what I was -- actually the second point of natural history of the disease. For example a bleeding disorder or any disorder if without intervention there is 100 percent rate of mortality and with the use of a product even if there is 50 percent or 60 percent, you know, prevention of that event I think that is stark enough evidence to show effectiveness. So, you know, sometimes an actual history of the disease if available is also helpful to act as an

appropriate control.

DR. GOLDSMITH: Okay. I think we will just go ahead now. Dr. Karen Weiss from CDER --- is going to demystify I think accelerated approval for everybody. Glad to have you.

(Adjusting equipment.)

FDA Perspective: Licensure of Products Under Accelerated Approval

Karen Weiss, MD

DR. WEISS: Yes, thank you very much for the invitation and, yes, I am in CDER, but that is a very recent event. I spent many, many, many, many years in CBER before the products that I am involved in, the therapeutic biologicals, were transferred from CBER to CDER, and that occurred a couple of years ago. So anyway I still sometimes forget which center I am from. I am very happy for the invitation and to be here today to talk a little bit about accelerated approval. My particular office has had some experience with accelerated approval, and there has also been a much larger experience in the center for drugs, and particularly in certain disease settings which I will try to cover very briefly.

(Slide.)

Highlights of accelerated approval, and Nisha Jain has already commented on and touched upon some of these

issues in her talk, and so that will be good to sort of emphasize things. Accelerated approval is sometimes a misnomer. I think a lot of people have difficulty with the actual terminology, accelerated approval, because in fact it is not -- I mean, it is accelerated in one sense, but not in the sense most people think about. An early iteration I think of this regulation, it was referred to as a conditional approval, and I think there were various reasons why in the early ‘90s this was changed to accelerated approval. But in fact it is an approval with specific restrictions or conditions attached to it, and I will mention that in just a minute.

It is a procedure or a regulation that is basically geared to those individuals who have serious or life-threatening conditions. I think a lot of the ones that are the focus of this conference would fit into that category. The therapy is supposed to represent or have the potential to be an advance over available therapy. Clearly if there is nothing available for the disease that is pretty easy to envision that it would likely or possibly be an advance over available therapy when there are lots of therapies available. Those issues might have to be addressed in the particular types of studies that are going to be conducted in terms of what is the appropriate control.

Primarily this regulation deals with studies that

have been conducted or are being conducted that look at a particular surrogate outcome. The regulation specifically states that the drug or biologic is studied in these kinds of conditions and that there is an effect on either a surrogate endpoint or other clinical endpoint that is reasonably likely to predict clinical or, in the case of the other clinical endpoint, the ultimate clinical benefit.

So the difference between approving something with regular approval versus accelerated approval, particularly when we are talking about a surrogate because obviously the agency has approved numerous products, blood pressure lowering drugs, et cetera, on the basis of a surrogate, the slight difference in this particular regulation is that the surrogate is not as closely tied with, linked with, validated, whatever you want to say, to the ultimate endpoint of interest. It is felt to be reasonably likely, and that is a bit of standard. In fact it is considered to be a lower standard. The level of assurance that that surrogate is actually going to be linked to and predict the clinical outcome is not quite as great as it would be if you were contemplating a regular approval; and the same can go with the clinical outpoint, the other clinical outpoint other than the final clinical endpoint of interest. We approve things all the time based on clinical endpoints, clinical benefit. That is basically the standard of approval, but there might

be situations where a particular sort of -- like for instance a short-term clinical endpoint may be important in its own right, but maybe not quite as strong and firmly believed to represent or to predict the ultimate endpoint of interest. Or there may be issues with risk and benefits and a short-term endpoint where short-term toxicity may not result in quite as favorable a risk/benefit ratio as one would like to see, and therefore it might be appropriate to grant an accelerated approval. So it is a little bit confusing because sometimes the surrogate or other clinical endpoint can be the basis for an outright approval, and sometimes it might be a basis for an accelerated approval. It depends a lot on many, many, many considerations.

The main restriction or condition of this type of approval is that the applicant conduct the studies post-approval to verify and describe the actual clinical benefit. One slight nuance, if you will, from what Nisha had mentioned -- and it is true that oftentimes you would like to actually validate the surrogate in this post-commitment trial or post-marketing trial. That isn’t actually required. The regulation specifically says to verify and describe its benefit. It doesn’t actually say validate the surrogate; and that is sometimes an issue because sometimes the post-marketing trials are very different trial design than the accelerated approval trial, and sometimes the surrogate that

was the basis for accelerated approval isn’t even measured in the post-marketing trial. So it is not possible really to validate the surrogate, and so -- and sometimes that becomes an issue with why or why not the verification trial may actually fail. In fact, accelerated approval has been in the lay press quite a bit lately, and not necessarily in the best light. There have been lots of concerns and discussions by outside people and particular in Congress about this particular mechanism.

(Slide.)

Okay. So post-marketing studies as already been alluded to are actually required. There are lots of post-marketing studies that are asked for at the time of approval, but the requirement to do these studies is actually only linked to a couple of situations; to pediatric studies that are required under certain types of provisions per the Pediatric Research Equity Act I believe it is called, and required under accelerated approval. The regulation states that ordinarily these post-marketing studies would already be underway at the time of accelerated approval. That isn’t always the case, and sometimes that is also the problem that Congress is being of recent note identifying with respect to these post-marketing trials, and that is basically the issue of due diligence. These trials are supposed to be conducted with due diligence, which is somewhat of a vague term, but

Congress is believing that many, many of these post-marketing trials are in fact not being conducted with due diligence.

This provision also allows for the agency to withdraw approval if the post-marketing study either fails to verify the clinical benefit or there is failure of due diligence, and there is a process for this. It is called a Part 15 hearing. At this point in time, that may change in the very near future, but at this point in time there has been to my knowledge no accelerated approval product that has been withdrawn from the market for one of these particular conditions, but stay tuned.

(Slide.)

The specific documentation for accelerated approval can be found in Code of Federal Regulations. There is identical language whether you are talking about a biologic under the 601 series or a drug under the 314 series. It is oftentimes referred to as subpart E if you have got a biologic and subpart H if you have got a drug. Specific discussions about this regulations can be found in the final rule which was issued December 11th, 1992, and I have the citation for that. There is also a very nice discussion in the fast track drug development program guidance document that was issued in 1998. Fast track was an outgrowth or part of the Food and Drug Modernization Act, FDMA, of 1997, and the latter half of that guidance document includes a very

nice discussion about what we really mean by accelerated approval and in particular the issues of approving something on a clinical endpoint that is not the ultimate endpoint of interest, and certain scenarios of why we might want to do that type of approval on an accelerated approval as opposed to a full or traditional or regular type of approval.

(Slide.)

So what has been the experience, and I have to start talking fast, in this? In the very first approvals using the mechanism have been in the HIV/AIDS setting, and in fact there is also a nice discussion if anybody would like to read it. That is on the bottom of the slide. It is a guidance document. The long and story short is that over time there has been an evolution in evaluation of data that indicate that viral loads, suppression of viral load through primarily a year's worth of study is very predictive of clinically meaningful outcomes including survival and other types of OIs and AIDS-defining events. So the agency issued guidance basically saying that clinical endpoint studies for approval of antiretroviral therapies were no longer necessary of feasible and that treatment-induced decreases in plasma RNA would be highly predictive of benefit and can be the basis for either regular approval or accelerated approval. If you are using accelerated approval basically the paradigm has been that short-term effects on viral load such as 24

weeks, sometimes 16 weeks, are predictive of longer-term effects in viral load which in turn has been validated as an appropriate surrogate outcome for clinical benefit.

(Slide.)

This slide is not all that legible, but it is just showing you. This is borrowed from one of my colleagues in CDER, a statistician, Dr. ---. It just shows you that the different antiretroviral drugs that have been approved from the -- it looks like 1990 on through 2001, there has been a dozen or so, and it shows a little bit of the time frame and the outcomes that were used for the accelerated approval and then subsequently the conversion, if you will, to the regular type of approval. I think the key point in this is that in the HIV arena these post-marketing trials are being completed, and there is a reason for that which hopefully I will get to at the end.

(Slide.)

In oncology there are a number of different types of endpoints and outcomes that are being utilized in different types of tumor settings. Clearly a direct benefit is overall survival or sometimes improvements in tumor related symptoms. There are a variety of surrogate endpoints including a disease-free survival, overall response rate, progression-free survival, and many of these have been utilized as indicators of clinical benefit, basically

accepted surrogates, and have been the basis for a regular approval. In other settings, other disease situations, these kinds of outcomes are considered to be reasonably likely to represent benefit and therefore have been the basis of accelerated approval with post-marketing trials. So it is a little bit confusing to probably many people because sometimes the same endpoint is appropriate for regular approval and sometimes it is appropriate for accelerated approval. Really that depends in great extent upon what particular disease you are dealing with, what particular cancer you are dealing with.

(Slide.)

This is a survey that John Johnson, somebody -- a medical physician in the Center for Drugs conducted. It was published in the Journal of Clinical Oncology in 2003, where he looked at just a survey of a number of oncology approvals over about a 12-year period of time and found that about two-thirds or so of them approval was based on endpoints other than survival, which is the ultimate clinical endpoint of interest. You can see that of the number of approvals a relatively small but --- proportion were done on the basis of an accelerated approval, and I will just move on.

(Slide.)

Some of the issues in use of accelerated approval are the difficulties in identifying a reasonable surrogate

endpoint, and in the setting of HIV/AIDS, in the setting of cancer, you have lots and lots of patients and the ability to do a lot of analyses of existing data to try to come up with what are reasonable surrogate endpoints. For many of the rare diseases it is much more difficult, and you will hear a case example tomorrow from Alison Lawton from Genzyme on what was done for one of the enzyme deficience disorders, Fabry disease. It is ideal if natural history data are available to help troll through some of these databases and help to identify perhaps some potential surrogates that can be done that are feasible to be measured and that might be reasonably likely to predict clinical benefit. One of the problems is that confirmatory trials may fail to show a benefit or they may result in an unacceptable risk/benefit ratio.

(Slide.)

That is two examples. One is Iressa which is a drug that was approved in Center for Drugs, an oncology drug that was approved for people with advanced small cell lung cancer. The first approval, which was in 1993, was on the basis of response rate alone, and the trial was not a control trial in the sense that there were two different doses of Iressa that were utilized, but there was no other control in trial. The trial was approved or the product was approved on the basis of an overall response rate of 10 percent, which was felt to be very good for this type of disease.

(Slide.)

What happened is that the company conducted a very, very large randomized placebo controlled trial in a very similar population, over 1,000 patients, and was not able to show an improvement in overall survival on this. You can see this on this Kaplan Meyer curve.

(Slide.)

Interestingly enough, in the same trial there was a measurement again of response rate, overall response rate. A highly statistically significant improvement in response rate, but that did not translate into a survival benefit; and this is one drug where there is a lot of consideration about what to do next, and one of the options could be withdrawing this drug from the market.

(Slide.)

Another situation that I was directly involved in is ---, which is a monoclonal antibody for the treatment of patients with multiple sclerosis. This is a finding from the trial. This was a two-year trial, but we believe that based on important outcomes at one year of duration of a two-year trial, which is a highly statistically significant reduction in relapse rates, that it would be appropriate to approve this product under accelerated approval mechanisms with the idea that the longer-term data would come and tell us whether or not this effect was durable and also to give us more

safety information. What happened was that there were cases of a particularly devastating neurologic infectious disorder, PML, that have turned up late in the clinical trial database, and this drug is currently on hold if you will. No patients are getting this drug and people in the clinical trials are being extensively evaluated to determine whether or not -- what the true numerator and denominator is with respect to risk for PML.

(Slide.)

Another issue in accelerated approval is the issue of confirmatory trials. I think the Iressa and the --- trials are great example of the facts that confirmatory trials have been done and have raised questions about appropriateness of having each of these products on the market, and those are going to be ongoing discussions. So to me that shows that this procedure and this mechanism actually works.

Ordinarily the confirmatory trial is underway at the time of approval, and in the HIV/AIDS setting, in the example with multiple sclerosis that I gave you that is exactly the case. In fact, it is the same trial. One sort of breaks into the trial early on and looks at an interim or surrogate outcome at a shorter time period while these data are being evaluated. The trial continues, and so it is relatively easy to have the trial continue and to get the

longer-term outcome. Cancer is a very different animal, and many times the trial that was done to lead to an accelerated approval is not the type of trial that can be done or can show really the clinical benefit. So new trials have to be developed in different populations, different types of designs, different types of controls. These are sometimes more cumbersome to get going. They are larger trials, and that I think is some of the focus of some of the criticism about these trials not being completed or not being done with due diligence.

So one take-home message that I have certainly learned over the years with this is it is very, very important to plan ahead for anybody who wants to think about an accelerated approval approach. Particularly it is important to think about what is a confirmatory trial, and if it needs to be a different trial it is very important to start the trials as early in the drug development paradigm as possible because it may be very, very difficult to actually conduct the trial, depending on what trial design your are talking about once the product is on the market. Like I said, there has been recent criticism by Congress and others about accelerated approval and the fact that these confirmatory trials may not be completed appropriately in an appropriate time frame, or there is also some criticism that we are not making transparent enough to consumers and

healthcare providers the fact that these products are approved under accelerated approval, that the standard is a little bit less, if you will, and that there are post-marketing trials. We had such language to some extent in our product labels, but those are always hard to find and people may not understand that. So that is sort of a two-fold criticism, very recent, and I am sure there is going to be further evaluation by Congress about this whole process. I think with that I think that is my last slide, so than you ever much for your attention.

(Applause.)

DR. GOLDSMITH: I think again we could probably take a question or two if someone has one about accelerated approval or how it might impact on these products for small populations. There we go. I was looking for the red light. I was trying to be trained to do this. Now I see it.

MR. CASTALDO: I was curious. You know we are in the post-Vioxx environment right now which many of us shake our heads at for a variety of reasons in our patient community anyway. I was curious in terms of what you have heard and what you have read about and many some contacts you have had from Congressional sources, committees, et cetera, and if there was any concern that filtered down to rare disease accelerated approvals.

DR. WEISS: Fortunately I guess I am not high

enough level in the agency to actually get the direct sort of Beeline from what Congress is saying, and hopefully I am low enough that I won't be hauled in to testify on anything, so there is some comfort level on that. All I can tell you is the same questions that you have actually people are saying the same kinds or raising the same kinds of concerns or anxiety as it relates to cancer. In fact that, gee, we are applying standards for very common disorders or maybe not quite as rare disorders or not quite as devastating disorders and we are going to be -- that the outside world and Congress is going to be using, you know, the experience with Vioxx and maybe the other types of diseases to put further restrictions on whether you are talking about cancers, whether you are talking about rare, rare diseases. I know those questions are out there. I can't honestly tell you what is going to happen, but I would think and certainly hope that people don't generalize from one particular setting to another setting. I mean, the whole idea with accelerated approval really started with the HIV/AIDS epidemic and the idea that you really have to get products out there sooner than ordinarily would be done, and I think in many diseases it has actually worked very well.

DR. GOLDSMITH: One more question here. Donna.

DR. DiMICHELE: The concept of a confirmatory trial I think is a very interested one, and I know that post-

marketing surveillance and confirmatory trials are discussed as different entities. Do you see -- and, I mean, it almost seems that with post-marketing surveillance that compliance is the biggest issue and almost has to me -- I mean, everybody mentions post-marketing surveillance in every one of their slides, and it just seems that it is the issue that stands to, you know, railroad this whole process more than anything else. So my question is can post-marketing surveillance be considered a confirmatory trial if conducted in that way?

DR. WEISS: They are really entities. I mean, normally when we think about the post-marketing verification trial we are really talking -- and generally these are randomized control trials. Many times they are a trial that is not necessarily more rigorous, but there should be the same standards that would be put into place for a regular approval, and post-marketing surveillance at least to my mind is a somewhat of a different entity. It is much more passive. There are lots of limitations to it. It is much more difficult to actually draw conclusions because you have to remember that in accelerated approval you are really trying to verify that there is clinical benefit. The post-marketing surveillance really has more of its role in, you know, trying to evaluate and bring to the forefront safety issues, particularly ones that you can see in a larger

population, ones with comorbid conditions, et cetera. Things that you really can't do in a clinical trials database because normally in a surveillance type of setting you are talking about putting it out there on the market to -- well, probably not for this population, but in a general sense you are talking about putting it out to many more thousands of people than you have actually been able to study in a clinical trial setting.

DR. GOLDSMITH: Okay. Thanks very much, Dr. Weiss. I think we will move on to the next speaker who is Dr. Lachenbruch from the Office of Biostatistics and Epidemiology in CBER. He is going to talk about FDA perspectives, statistical considerations for very small clinical trials.

(Adjusting equipment.)

FDA Perspective: Statistical Considerations for Very Small Clinical Trials

Peter Lachenbruch, PhD

DR. LACHENBRUCH: I think I would like to add one small item to Karen's response, and that is eight or nine years ago I examined the completeness of coverage of the post-marketing surveillance in VAERS, the Vaccine Adverse Event Reporting System, and found that about one-third of the deaths were captured. There was the VAERS and we also had the vaccine safety datalink where we had some stuff, studies

with some HMOs. About one-third of the deaths were found, about one percent of the other -- the non-serious adverse events, so I think you can't really rely on the post-marketing surveillance as a system to validate things.

Okay. Well, quite obviously there are two people on this presentation. In the program it says that Dr. Ng will be speaking. Even my badge says I am Dr. Ng. I am not. I am Dr. Lachenbruch.

(Slide.)

Okay. Well, questions, why do we do small clinical trials? What can we do if we have just a limited number of patients to enroll in the trial? One of the things that we could do is change the standard to a one-sided 0.05 test. That means we are still making a mistake five percent of the time when the null hypotheses is true instead of two-and-a-half when we do the two-sided. Strategies may include some more efficient use of the available patients, including different endpoints, different designs. Basically the bottom line comes down to we have a very small number of patients available to do these clinical trials. I remember one study I believe, Karen, you were still at CBER on the osteo --- trial, in which they got every patient in the world for this disease and actually did a two-arm study. I think it was about a two-to-one randomization, 16 to 9, and they actually -- hmm? 16 to 5, thank you. You know how it is when you get

old and your memory goes. Anyway, they actually were able to demonstrate a survival benefit in this disease, but this is very, very unusual.

(Slide.)

Okay. As you have been hearing again and again, we need adequate evidence of safety and efficacy with what we know to be limited information. Rare diseases, typically the patient population is going to be fewer than 1,000, frequently in the 10s to 100s in some of the things we saw earlier this afternoon, and I must apologize that I missed the morning. But they were talking about 500 patients total in the US, and if you think about it when we go to major centers we may find only 100 to 200 patients available. Our inclusion and exclusion criteria may reduce the population available by 50 percent. That is pretty much of a typical thing in my experience. Then if we have consent issues that may reduce us by another 50 percent. So we are down to perhaps a maximum size, sample size, of between 25 and 50 patients to conduct a trial in. Sometimes stakeholders, the foundations, the patient groups, may be able to encourage people to volunteer for clinical trials, but that, we are still talking about a very, very few patients.

(Slide.)

Should we apply the same standard -- I mentioned

this earlier -- and hope to find a very large treatment effect? Should we change the standard to a one-sided 0.05, slightly lower level of evidence, or reduce the power which reduces the sample size, but this in effect gives a greater risk of a failed study. Basically if you think of a power of 80 percent, that which is quite common, that means that 20 percent of the time when there really is an effect of the size that we think it will be, we are going to miss it. Well, if you say we are going to reduce it to say a power of 50 percent, which as a statistician I would not recommend, but if you say we are going to reduce the power to 50 percent you may be able to do the trial, but you are still likely to -- what this means is only half the time when the effect is real are you going to in fact detect it. I suspect that most pharmaceutical companies, biologics companies, are not going to like those odds very much. I certainly wouldn't.

(Slide.)

So what do we do when we have limited numbers to enroll? More efficient use of the available patients is what we are really trying to do, and so by changing the endpoint we may look at say a clinical endpoint which is success or failure. Now sometimes success or failure is did the patient die or not. That is a commonly used one, but there may be others that could be done. Serum plasma concentration is a surrogate, or times to events. So we have options here, and

what I would say to drug company sponsors or any sponsors is that talk to the FDA and talk to the clinicians. A statistician may be able to say, yeah, that sounds like a cool idea, but if the clinical reviewers are not happy with that no matter how happy I am or somebody else is, some other statistician, it is not going to fly. So talk to the FDA early and often, and the other item I would say along this line is be as transparent as you can. Don't come and hide stuff from it because sooner or later it is going to come out.

(Slide.)

What can we do with limited patients? Well, this traditional design is a two-parallel group design. So you have the one group gets a new treatment and the other gets a standard. By the way, if we say placebo or control, we almost always mean standard of care. We don't mean the patient gets nothing. Sometimes that is misunderstood by the general public, the press, or Congress. Paired data meaning that we will find a match to the patient say by age or gender or both, and this can be very difficult to impossible, particularly when we have a very rare disease. You don't find two patients showing up essentially at the same time or very close to the same time. Crossover studies are possible. That means a patient will get one treatment for a while and then move to another treatment, and that would be a

reasonable thing, but it isn't possible if the treatment permanently changes the patient. For example, in a vaccine study you can't do a crossover trial because it will generate immune antibodies.

(Slide.)

Other kinds of endpoints, continuous versus binary. So binary means did the patient improve or not improve, was there a success or a failure, or continuous variable such as plasma concentration of a product. We can look at tolerance intervals which can show that a fraction of the values of the variable lie within acceptable range. This is I am afraid not likely to be that fruitful because it typically will require a much larger sample size than you would want. For example in this case you would have a serum concentration after treatment of 40 percent with a 15 percent standard deviation. Well, the confidence interval says let's look at 40 plus or minus 1.96 which is the usually Z value times 15 over the square root of N, 15 being your standard deviation. Tolerance interval will use 40 plus or minus some other number K times 15, where K depends on the confidence and the fraction of the population to be covered. You are trying to show that most of the population relies within certain limits, and the tolerance intervals always are referring to a population while the confidence limits refer to statements about a mean value.

(Slide.)

We can look at longitudinal versus fixed time. So we could get multiple measurements from each patient, and this only will work partially. So it would be nice to be able to get 100 measurements from two patients, but that ain’t the same as getting four measurements from 50 patients. I think we would all be much happier with something like that. There are some statistical models that are available that have looked at these things. When I first started out in statistics all these many years ago we didn’t have such tools. People were thinking about it and trying to say how in the world are we going to do this. Well, the GEE models were developed only about 15 or 20 years ago. We can also look at averages, and the issue that we have with averages is that because the measurements within a patient are correlated, it is having five measurements within one patient isn’t like saying we have five independent measurements. Typically measurements within patients, in my experience they seem to have correlation somewhere around 0.5, so it does tend to reduce the amount of information as you go. So when you get out to looking at 10 or 15 measurements you have probably reached the point of diminishing returns probably even before that.

(Slide.)

Last week Nisha and Mark and I think John and I and

Tie-Hua considered the situation of the thrombotic prevention of thromboembolism in the at-risk ATIII deficient patients and learned about what that really means just now. So the clinical endpoint is no TE for each pregnancy, so it is going to be difficult to generate very much data when you consider that each pregnancy is going to take approximately a year to be complete. If we wanted to get three measurements from each patient we are talking about a minimum of a three-year study, and that is unlikely to work. So you might consider a case for a one-arm study to beat some sort of a standard, and I have heard that, the standard, referred to as a hurdle or a belt line. Basically we say, okay, we know without any treatment we would have perhaps 50, 60 percent of our patients having TEs. With this if we can cut the number down to five percent we can say does five percent beat 50 percent. You bet it does, so we could look at that. Alternatively we could look at the plasma levels and use an interval to show that 95 percent of the population is above 100, or use a confidence interval to show that the mean is above 125. These are numbers that I have pulled out of a hat. They are not FDA policy. Please, you know, everything I say is coming out of my own imagination and not out of any FDA policy, so please don’t say, "I heard Dr. Lachenbruch say that the requirement for FDA is such-and-such." It ain’t.

(Slide.)

We can reduce the measurement error. So if we get multiple measurements within a relatively short time period. For example, to do this we need problems that will recur. For example, bleeds in hemophilia. Now that is probably not rare enough for this conference. We can perform replicate assays. The problem with this is the cost and facilities are major considerations. The last bullet on this is to remember that the unit of analysis is the patient, not the visit, not -- and as I said earlier, 100 times 2 is not the same as 4 times 40.

(Slide.)

Surrogates or alternative endpoints which Karen was talking about are possibilities. So we could look at plasma levels versus success or failute. Failute? Okay. Good. We now have a brand new word in the language. It usually gets us a tighter comparison, but there may be a question of whether this actually represents a clinical benefit to the patient, and so when this happens we usually have some long discussions internally and then we have some long discussions with the sponsor about all of this.

(Slide.)

Designs. The ICH E10 document discusses all the possible control groups including use of historical data. We can compare a product to a standard or treat the historical data as if it were a pseudo arm of the trial. I

think it is most useful if the outcome is uniform and known. Also you want the historical controls to be fairly close in time. So getting a data set that was collected from 1970 to compare to a study that has been done 2005 is going to be difficult for to justify simply because the standard of care has changed. Parallel versus crossover we have talked about. Obviously it is feasible only if the treatment doesn't cause some sort of a permanent change, and we talked about immune status, but death is another one. If you have a patient that dies on the first arm of the study it is very, very difficult to get any further data.

(Slide.)

So why do we have small clinical trials? The answer is that we don't have sufficient patients in the population. It is not "I don't want to do a bigger trial." That won't get a lot of sympathetic ear in this. Consider use of surrogates, PK, other alternatives. You can look at crossover studies, single-arm or one-sided tests.

(Slide.)

The top bullet here is essentially what I have been saying. If the patient population is quite small we are extremely limited in the trials that we can conduct. Dichotomous, that is yes/no, success failure have relatively low power compared to a study in which we have a continuous endpoint for which we can have a small variance. We should

consider longitudinal studies and crossover trials when they are feasible. Da-da. Done.

(Applause.)

DR. GOLDSMITH: I think we can take a question or two. Down here in the front.

MR. : I have a question that I have always wanted to ask in relation to statistics and rare diseases, and I hope that you will consider it interesting rather than ignorant.

DR. LACHENBRUCH: Don’t call me. I’ll call you.

MR. : And that is why do we need statistics in rare diseases in the sense that much of what statistics is trying to do is evaluate whether a sample population is representative of an entire population, and many -- in many diseases we are actually evaluating the entire population when we do a study.

DR. LACHENBRUCH: Okay. Very fair question. I don’t have a great answer, but as you say if we have the whole population you have the answer. The question that also comes up is is this going to be predictive of what will happen in the future. So you have got the whole population in 2005, but it may be that this year happens to be a little bit different from next year or maybe a lot different. For some reason something odd happened. So that is one reason. Another reason is that you probably don’t have the whole

population because you are inclusion and exclusion criteria are going to get people out of that. Now you can say the trial really should apply only to the people that meet the inclusion and exclusion criteria, but then you also have the issues of consent. If you have lost people because of consent that is another -- we would like to generalize if we could. We are not always lucky. I hope I have given you a start of an answer.

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

DR. LACHENBRUCH: Thank God. Full employment for statisticians.

DR. GOLDSMITH: Any other questions? Okay. Thanks.

DR. LACHENBRUCH: Thank you.

DR. GOLDSMITH: Okay. The last talk in this session is by Dr. McCormack from the Office -- from the Orphan Products Development. He is going to talk about FDA perspectives of current regulator incentives for orphan drug provisions, and he is a great friend I think to many of the stakeholders here.

FDA Perspective: Current Regulatory Incentives Orphan Drug Provisions

John McCormack, MD

DR. McCORMACK: I guess I just want to start off, you know, by announcing that my talk has already been given

by about three people, so there is not a whole lot of sense continuing it. So at any time if somebody wants to stop just holler, you know. Let’s see. What did I do wrong? There we go.

(Slide.)

I guess the -- that is me. What I would like to start off with here is the first immutable law of drug development.

(Working on equipment.)

Okay. Thank you, and that first immutable law is no profit, no drugs; and that is one of the major problems that this population has to deal with is that with the size of the population it is very difficult for pharmaceutical firms to cover the expenses that are necessary to go through the development process and still make a profit.

(Slide.)

My daughter is a finance major, and she informs me that this is an extraordinarily naive approach, but it is my way of thinking of it. The one thing that I wanted to point out is that there is something on the top and something on the bottom, and what that means is both of those things are manipulatible. It is an equation, just that simple, and if we look at profits for instance, now, there are a number of things that make up what that is going to be. Obviously one very important one is the size of the population that is

going to comprise your market, and that leaves us out of the picture totally. The second one is actually if you think about it is the quality of the product, because people will pay a lot of money to live. People will pay a lot of money to be free of their disease. They will pay a lot less money for what I like to characterize as a hope drug. So that is another major point to consider here, and of course the last one is the price of the product, and the quality of the product can really determine the price of the product. I always tell pharmaceutical firms you can make money on anything if you charge enough for, and for the orphan community the fact you want them to make money on it and so if they have to charge a lot to do that then do it because we want product, and that is our big push.

(Slide.)

Now cost of development as we have heard is another one you can break down into a lot of components. Basic research, clinical research, as was pointed out this morning the cost of money. Given the risk of the project involved, what sort of return do people need for that? Another one which we at the FDA certainly contribute to I think out of necessity, but that is something that we always have to ask ourselves, is regulatory costs which can be significant. Of course the list goes on for days, hours, whatever.

(Slide.)

Now the point is that each piece of the equation offers opportunities for intervention, and that is sort of the basis of the Orphan Drug Act, and we go through and just see what are the options and then look at how the Orphan Drug Act does it.

(Slide.)

Profits, well, you know, one of the ways of increasing profits obviously is to give out intellectual property rights. If I can limit the competition I can keep the market intact, therefore I can increase the number of patients that are available or customers that are available to the person holding the patent or holding some sort of exclusivity. So that is one that our society has found very important, placed a lot of emphasis on. It is also one where when people exploit the monopoly we give them we also tend to get a lot of feedback on because I don’t -- you know, what you hear is "I don’t understand why there aren’t more people in the market." The reason there aren’t more people in the market, the reason the price is as high as it is, is because we are trying to put people in a position like that so that they will develop new products.

(Slide.)

Now, it doesn’t really apply here a whole lot, but it does if you look at the problems we are dealing with long term. You know, we don’t want to give these people

fractionated products for the rest of their lives. What we would rather do is fix them, and so maybe the long-term approach to this should be finding a way to fix them. If you look at the resources we have available here, certainly NIH does an awful lot of research, spends an awful lot of money. There is no reason why they shouldn't be looking at a way to fix them. With grants, our office gives out grants. Numerous patient groups give out grants. Certainly the NIH gives out a ton of grants. Again, that is a way to try to lower the cost to any manufacturer by doing their basic research, their development work, for them.

(Slide.)

Now, clinical research is the big kahuna. It is the thing that probably limits products coming on market more than anything else. It is by far the most expensive thing a manufacturer -- that a sponsor does or a manufacturer does to develop a drug, and the ways that we can affect that are pretty obvious. We can give grants for people to do for studies, and something else that we can do is we can give out tax credits or just allow them to deduct the cost of the studies as a business cost, which effectively means that the taxpayer is picking up somewhere between 25 or 50 percent of the study depending on where it is done and what provisions they use. But the other thing, which was just the last two talks talked about that really is very important I think, is

developing some way other than our classic way of thinking about clinical trials or our classic way of measuring results. We have to find a way to change that somehow because if it is going to cost you -- oh, let's just say I think the number $25-million was mentioned earlier, to do a clinical trial in 75 patients, and your market is maybe 150 patients, then you know you are really talking about a lot of money up front. So while we can pick this up with our tax credits or mitigate the effects with tax credits and grants, we still have to recognize the inherent problem that the industry deals with trying to get around this.

(Slide.)

Now there are also regulatory costs, and in my time at the FDA the FDA has added to those with what they now call user fees, and certainly a regulatory cost if speed of review. The longer that an application sits at the FDA, the less money that can be made by selling the product out there. One of the things I think that FDA need to be very, very sensitive to is what I like to call need to know versus nice to know, and especially in these kinds of diseases what we need to do is keep it down to the essentials. There are lots of instances where I would feel much more comfortable having information to make a decision on, but the question I have to always ask myself is is it essential for the decision, and if it isn't, especially in these types of applications, you just

got to go with the what you need to know.

(Slide.)

Now let’s take a look at the Orphan Drug Act. How have we approached the problem? Well, first we start off with probably our biggest incentives, seven years of exclusivity. What we are trying to do is to keep the market whole so that somebody who goes in there and gets it gets the whole market. They get all of the money out of the market. So we are trying to increase their profits. The one significant thing about it is to remember our exclusivity is by drug, by disease. Which means you get essentially the same thing as a use patent. You get exclusivity for a particular drug for a particular indication, and the other thing about it is it is only seven years, but it starts at the time of FDA approval, which usually -- you know, I think patent life is now 20 years, 17 years, something like that. You know five or six of those at least are taken up in development of the drug so that it is about two-thirds of a patent when you take a look at what you actually get.

(Slide.)

Now, another thing that we try to do in the Orphan Drug Act is to lower the cost of clinical trials, and the way we do that is we have tax credits which are 50 percent of all costs incurred for clinical trials, clinical meaning in a person. They can be PK trials, they can be efficacy trials,

but they have to be in a person, no animal studies, and it is 50 percent. The other thing is for start-up companies we give them a 20-year carry forward or a one-year carry back, which means they don't have to be making money at the time they do the clinical trials. They can build equity with these and it is something they can always use to value their company if they were going to sell it or something like that.

(Slide.)

And for the regulatory costs we have user fee waiver, but the one problem with it is it is only for application fees and it doesn't cover establishment or product fees. Now establishment and product fees can be waived individually based on small business criteria and other sorts of things, but you don't get an automatic waiver with the orphan if you are an orphan. However, the application fee is at least $600,000 right now, so that is a pretty good chunk of change that the FDA is waiving.

(Slide.)

This is something I think that -- this was a major part of the original Orphan Drug Act in 1992 because it was very difficult to talk to the FDA at that time, and so what this did was it gave you the right to ask the FDA if a trial design was acceptable, and if the trial worked and you showed that you demonstrated efficacy then they were required to honor the trial. Things have changed a lot and there is now

something called special protocol assistance, which is pretty much the same thing. But every once in a while when our office is shepherding a product through, you know, just trying to provide a little help, we run into a little resistance on sort of coming up with a design or the review division coming up with a design that they are really willing to stand behind. So I am thinking that we are probably going to start to see a little more written protocol assistance in the future.

(Slide.)

Grants, and for the academicians in the group we have the grants are only for clinical trials. It is $200,000 for a phase I. That is total cost. We used to do just direct and didn't pay any indirect, but it was really limiting the number of trials that we could fund by doing that so now we are giving total costs, direct and indirect. It is $350,000 for phase II or phase III. Now these are three-year grants that you don't have to compete. You don't have to compete for three years. You get $350,000 a year, so that is a little over $1-million for three years.

(Slide.)

This is our website. It is a good website and all the information you need is on there, and the dates -- well, the RFA is always on there for the academicians and anybody or any company that has any questions just -- you know, most

of the time they are answered on our website, but if they aren't feel free to give our office a call. Anybody in the room feel free to call our office. We are happy to talk to you, and I guess that is it.

(Applause.)

And I guess the one thing I would say is when I look at the incentives of the Act and how much they can contribute to the problem I think we are pretty well maxed out and the problem hasn't gone away So it is going to take a little more, you know, a different approach or something.

Open Panel Discussion

Jonathan Goldsmith, MD, Session Chair

DR. GOLDSMITH: All right. I guess I would like to invite the speakers from this afternoon to the panel, and also the last speaker from this morning, Dr. Seitz. I think I will take the chairman's prerogative and just say a few words to kick this off. I am not an expert. I am from in town and I have no slides, so -- but anyway, I will give my two cents. The session here was about opportunities. It seems to me one of the things we talk about is creation of opportunities. We have heard a lot of things I think get at that, but we might want to verbalize some of it as we go along.

Here a few ideas that I have and I think we will get back to these. One is the role of establishment of a

patient registry at least to find some study cohorts. It might make it possible to do research when you couldn't do it normally and form a very important part of the infrastructure of these types of opportunities. I think we need to define the disease states. There are so many we are talking about today, but each one must have a set of definitions, natural histories and criteria. They are something akin to practice standards, something that might help define these in the public domain, and that I think would help other people to think about them if they develop clinical trials. One of the ways to learn something about diseases, this was done in the past for immunoglobulins, was to go back and review hospital charts and to learn something about the natural history of the diseases, how many infections per year do people have. It gave you an historical measure that you could then use as you came forward with a revised design for trials. Also you ought to find out really why you are treating. You are treating for short-term benefits, long-term benefits, something else. What is really the goal of the treatment design and be very clear about that so we don't get lost along the way. Dosing we have heard about from many people so far. How do we dose these disorders, what is enough and so on. I think that has to be if you don't know the answer from some sort of care guideline you have to go back and do dose ranging it seems to me.

Then two kind of big thoughts and then I will turn this over. Mark had a question he was going to bring to me and then others. How do you maximize information from small patient cohorts? You have to dig a very deep mine here, not a shallow mine to figure out what is going on, and you have to be creative to do that, so how do you make that opportunity? The other is can you think out of the box. We are thinking here about biologics, licensed biologics and so on. Is there any kind of interim strategy until these things come along? Is there a way to use something like plasma to treat a lot of these disorders, or screen plasma or a dedicated system of donors that might be available who have been heavily screened? Like may people in the family if it is not a dominant trait who might serve as donors for some of these patients in families. For some of the coagulation defects we don't really need to raise the level of the clotting factor very much to have hemostasis or to treat a lot of the problems. It doesn't answer the problem of GNPs or portability, access to these things for emergencies, but it may be an interim strategy. I just recommend that to some of the stakeholders to think about.

Okay. I think I have said enough and now I guess I would like to turn over either to the members here if there is something they wanted to follow up on, or I will provoke them if they don't say something spontaneously. They are all

ducking at once. I think statistics is always a good place to start because, A) Tony is a nice guy, and B) we don't understand it very well, so it is always good to go back to him. I think you talked in a general way about the use of model and the kind of concessions that could be made and what the costs might be. Is there anything that you can think of in a very specific way to help people if they plan some of these trials? There are some agents that have been licensed in Europe that we heard about earlier today, and is there anything that could be transportable into the US market?

DR. LACHENBRUCH: Well, I missed the morning session because I was at a different meeting. I am sorry that I did. From what I saw it sounded very interesting. I wrote down one item here which I think we need to keep in mind which is basically the more information that FDA and the sponsor have jointly before the trial begins, the better we can work together on designing the trial. Sometimes we will have information within the agency about products that are similar, obviously not identical, but we will have some experience with what problems other sponsors have had. We won't be able to tell you specifically what the problem is, but we might say think about X, Y, or Z in designing your trial, and usually that means we have got something in mind. We may not be able to be explicit about everything, but we will ask you to think about it. In terms of prior

information from other sponsors' trials if they have been licensed usually there is some information that is available to the public, and that should be exploited as much as possible, and basically everything is going to depend on the product and indication.

I did want to make one comment on John's statement which in turn has to do with orphan exclusivity as I recall. There are rules for when a product can be superceded if there is a better safety profile or better efficacy, and you may want to say a few words.

DR. McCORMACK: The orphan exclusivity is only available to the first product developed. Well, the first product that has the same drug and the same indication. If there was a drug on the market for instance where it did not have orphan exclusivity but it were approved for that particular indication then we would no longer give orphan exclusivity unless you could show that you were a better drug, and if you are a better drug that makes you a different drug, even though you might have exactly the same active ingredient. What that is is an attempt to try to allow for better formulations. Not different formulations, but better formulations to come on the market. So the criteria that we use, the three criteria, are either more efficacious, you are safer, or there is a third category which is called the major contribution to patient care. I think the one time that we

have found that a drug made a major contribution to patient care was whenever a particular product was given four times a day by injection and somebody developed a product that was given once a month by injection, so we said this is definitely a major contribution to patient care. Other times we have seriously considered it is for instance going from parenteral to PO. Those are the kinds of differences that we feel make a major contribution.

DR. GOLDSMITH: Let me ask -- well, okay. There is one thing I am going to try to throw out here. There are a lot of people from the manufacturing side here, and as you have heard we are all governed by laws and codes and things like that so we have a certain amount of decision-making abilities and actually fairly little latitude in the grand scheme of things from what I have heard. But if you had your day as a manufacturer, what would you change in the US code? What would you change that would then be new law for developing some of these orphan products? There are a lot of you out there. Here is a bold person.

MR. : Okay. Coming from the European side and considering of course for instance the tax exemption or the tax refund --- for US companies, and the main point that we can have in mind regarding the fact to be able to bring the product to market in the US is a kind of regulatory constraint that I didn’t see in the presentation, which is

linked to the plasma origin. You know that any blood product that is entering the US should be manufactured out of US-approved, FDA-approved plasma origin. So maybe it is also a reason some people can think about if a product of added value for a rare bleeding disorder could be introduced and if for instance it could be a very difficult point to overcome, For instance ---.

DR. GOLDSMITH: Would anyone like to take that? Nisha, would you like to say something?

DR. JAIN: Well, you know, apart from the restrictions to the source plasma used for the manufacturing of the process --- US source plasma or not US source plasma. But apart from that, I put up a slide saying that we are willing to accept any foreign data related to that product if it satisfies the regulatory provisions provided in the code of regulations. Does that answer your question?

MR. : No, not really.

DR. JAIN: Okay. Sorry. I think I misunderstood your question. Could you please repeat the question?

MR. : No. My point was to answer the question of what could be modified in the US regulation or --- that could ease the access the patients to some new products. So I was just quoting these restrictions in terms of plasma origin as a possibility to improve the access. So that was ---.

DR. GOLDSMITH: Let me let Jay take this.

MR. EPSTEIN: Under our laws blood or components to be imported into the US must either meet US standards or otherwise be found acceptable by the Secretary of HHS which is delegated to the FDA. So our law does not actually preclude the use of non-US plasma. However, it puts a high standard in place whereby we have to determine that we are taking product that is no less safe, and the difficulty that we have as a matter of practice is that it can be very difficult to ascertain equivalent safety of raw material because you have differences in epidemiology of transmissible diseases as you go from place to place around the world and also generally the question arises on the different quality and quality assurance of tests used to stream donors. So in a certain way Nisha's answer is pertinent because it comes down to the assessibility of the evidence and it is simply something that is hard to do, but it is a question practice and not actually law.

DR. GOLDSMITH: Peter.

MR. TURNER: I guess as a manufacturer, Peter Turner from ---, one of the issues that we have come across is the changing standards causing all clinical data to be rejected, and essentially I guess most people believe the product works, but it needs to be reproven again with all the modern statistics and all the modern protocol that now

exists. I am not sure with rare diseases whether this is truly adding value. I will give you an example. I think it is generally accepted that plasma exchange works in a lot of neurological conditions, and people use albumin for years, but there is not a clinical documentation of that particular technique that would stand scrutiny today. And if it becomes a standard for some other treatment then it potentially can get rejected because it doesn't meet today's standards. I think anything that could be done to alleviate some of these type of approaches could help, because companies face the issue of reinvesting in products that they are not sure there is a huge market for and if you do it on today's standards you are going to spend a lot of money.

DR. GOLDSMITH: Are we talking about clinical data or manufacturing information, --- information?

MR. TURNER: Clinical data that wouldn't -- it doesn't meet today's standards because certain regulations have changed, yet the product has been shown historically to be efficacious in other regions.

DR. GOLDSMITH: Okay. Any thoughts?

DR. WEISS: I just want to clarify, are you -- so is your thought then that you would like to see -- be able to collate all that historical experience, if you will, and submit it to a regulatory authority and believe that might be acceptable for approval? Is that --? Because I wasn't sure

if that was your question or if your question was being able to use some of these other methods as a control if you are talking about standards, so I wasn't sure what your question was. But if it is the former issue then being able to collate many, many years perhaps of data and experience to submit to the agency as a potential package for a licensure?

MR. TURNER: Yes, that is exactly it. In our experience sometimes that will work and sometimes it doesn't, and, you know, it is a difficult issue.

DR. WEISS: Just from some of my experience in some other settings, just it is a hard -- you know, there is a vast amount of belief that something is effective, and it very likely is, but you are right. Sometimes the standards aren't up to what the agency would like to see. It is very, very difficult, though, to go back and sort of retrospectively collect data that has been developed over many, many years, maybe decades, with changing, you know, standards of care, with varying methods to -- you know, whatever it is, collect or to process the plasma if that is what needed, or to have patients evaluated and screened. It just it is not completely unheard of, but it is just extremely tough to do that, and I can sympathize because -- but many times in those situations, you know, hopefully there could be ways perhaps to work with a small company or whatever to see if there is a way --- what things might be

acceptable for efficacy to prospectively collect a certain series, if you will, of patients all treated in the same way, all evaluated in the same way, building on what was known from all that prior history.

DR. GOLDSMITH: Dr. Jain.

DR. JAIN: I was just going to follow up on Dr. Weiss' point that it is very difficult to base anything on retrospective data. However, as I give in one of the examples, that --- was approved on a retrospective collection of data, only because the evidence of effectiveness was so strong and the period for retrospective collection of data was not a very wide period of retrospective. I mean, it was a very narrow period, plus the collection of that data was done very systematically by the Canadian authorities, so that was the basis of that licensure.

MR. TURNER: I guess I am saying this would help, and I guess whoever was saying before, I think it was Dr. McCormack, that, you know, the big kahuna is clinical, is 100 percent right. You know, when you are talking about rare indications with very limited markets, clinical is the stumbling block.

DR. McCORMACK: I guess our office has certainly tried to help people put packages together from retrospective data or clinical trials that were done significantly in the past and that sort of thing. Not under IND, just as a, you

know, academic study, and just finding the source documents is almost impossible and you really do need to go by more than just a generally recognized benefit to a therapy because we all know that George Washington was killed by his doctor. You know, not by the disease, but they bled him to death, which was certain the generally recognized accepted method of therapy.

DR. GOLDSMITH: Here, Dr. Seitz and then Dr. Casper.

DR. SEITZ: Maybe I should say in Europe to a certain extent we are quite lucky that we had many of these products on our markets since the ‘70s, so we have very old licenses for that and in those times there were no requirements for clinical studies and the material for these licenses was not so very strong from the clinical standpoint. Now we were obliged to renew all these old licenses because they were, if you want, preliminary licenses and now in the process of European harmonization we had to renew those licenses. I am not aware that we demanded very much new clinical studies for that, and we retained most of them, but we were lucky because these products were on the market from 30 years ago and nothing happened and everybody is happy with that. So probably a different situation in Europe.

Coming to the albumin or course albumin is a special story because albumin is given older than that and

was always seen as a very good thing, and then this unfortunate --- review came up and then we noticed that we are practically without good clinical data for albumin. Now we have a safe study which is very interesting and very convincing, but also the safe study shows us only that albumin is not dangerous and has no excess hazard compared with saline, but it does not show that it has excess benefit compared with saline. So as to the benefits of albumin we are still lacking a lot of evidence, and what we did in Europe is to amend the core SPC, and the core SPC says that the indication is volume replacement. The example you showed us, plasma exchange, is certainly kind of volume replacement, so you can do it in Europe. I don't see a problem there.

DR. GOLDSMITH: Dr. Casper.

DR. CASPER: I wonder of the manufacturers of plasma products to what extent is fear of recombinants an impediment to the development of new plasma-derived products? I would have thought that there was some low-hanging fruit. I thought that the factor VII concentrate made by Immuno in Austria would have been low-hanging fruit when that company was brought by Multinational because it is a GNP facility, the viral inactivation method is the same as used in ---, which is licensed in the United States that could be made from American plasma and get past all of this where does the plasma come from issue, but it wasn't pursued. Yet that is

one of the more common of the rare clotting factor disorders, and I wonder whether any manufacturers would care to speculate because -- not on factor VII, but in general. Because it looks to me the way the Orphan Drug Act is set up if some -- you have seven years exclusivity, but if somebody comes along with a so-called safer product and a lot of that would be the claim for any recombinant, then your scooped and you can't go forward. I wondered whether that kind of change to the orphan drug that includes the recombinants, you know, you can't claim a recombinant is safer, or is this the problem to the plasma manufacturers?

DR. GOLDSMITH: Anyone care to take that on?

MR. : I guess I will answer. It is a competition like anything else, and so you take all competition into consideration. I wouldn't say referring to the sorts of decisions we are talking about today it is a huge issue.

DR. GOLDSMITH: Then Dr. Soucie I think had a question.

DR. SOUCIE: Mike Soucie with CDC. I wanted to go back to in respond to a question from Dr. DiMichele of Dr. Weiss. The question under accelerated approval of whether post-marketing surveillance might be considered to be the same sort of thing that you were talking about, an extended clinical trial, and I thought what I heard was

references to really sort of passive surveillance systems for adverse events being equated to post-marketing surveillance. I am just wondering if that was the case or maybe I misinterpreted what the statements were, but we are going to be talking more about those kinds of things tomorrow I know, but I just wanted to make sure we were talking about maybe the same thing. I mean, post-marketing surveillance in an active way with clinicians providing data, clinical data on treatment of their patients and outcomes associated with that in a prospective way in a surveillance system as opposed to just passive reporting of adverse events if that is what we were talking about.

DR. WEISS: Probably should ask the person who asked the initial question to clarify, because I had answered it in the way you are saying, that there are different -- I was thinking of a prospective randomized control trial to meet the standards of adequate and well-controlled looking at a clinical outcome as the type of post-marketing verification studies that would be necessary under the accelerated approval provisions generally. That is usually what is the case. The simplistic way in the HIV setting was basically just continue out that same trial that is a randomized control trial. There are times when we look at things like -- and maybe some of this is terminology such as registries where you are prospectively collecting information on, you

know, additional individuals that receive the product post-marketing. But again, you know, the hallmark for accelerated approval is that you actually have to verify and describe benefit, and so to whatever method you can do that, that is somewhat vague, but in general -- and it also depends on what disease you are dealing with and what outcome you are trying to look at. Certainly in the oncology setting we have determined that for most of the diseases one would need to do a concurrently controlled, active controlled -- using a concurrent control, whether it is, you know, active control or an add-on placebo control, whatever. A specific type of design that allows you to draw these conclusions, --- conclusion about the clinical efficacy, the effectiveness of the product. I don't know if that helps you.

MS. : It has been my experience there are a couple of people in the audience who could probably speak to this better than I, but our experience with registries has not been all that happy. It is not easy to set up. It is not that easy to follow the use of the product. It is not easy to capture all of the information that would be needed for the kind of information that would be needed for accelerated approval. We have tried and we have a couple of examples here for some of our products where the experience is not fully satisfactory for that purpose.

DR. GOLDSMITH: I think Donna has been wanting to

ask something for a long time. Donna DiMichele.

DR. DiMICHELE: Well, first of all, let me just clarify this issue of the post-licensure surveillance. I mean, the reason I asked the question is that the clinical trial design for some of these rare bleeding disorders might be different and it might be single arm, and post-marketing surveillance could be considered in the same light in terms of an extension of the single arm efficacy and safety data collection, but done in terms of a study, a long-term study that could actually ensure that the data, you know, a lot better data and just adds to the original database. That is what I was thinking of, but anyway that is just to clarify for Dr. Soucie. So I would agree that, you know, I think it may be able to be done in a much better way than it is being done now.

But I had two questions, and the first was actually in the same vein. I was, you know, looking at the options for rare bleeding disorders. There seem to be several that the FDA has put forth today, and I was just wondering if the panelists could just comment on to what extent these initiatives, whether they be orphan drug or accelerated approval, are actually being used by industry. The corollary question to industry would be, you know, despite these measures being available to you, what do you find are the barriers to actually using them for some of the purposes that

we are talking about today?

I guess my second question was to Dr. Seitz who is the lone person representing Europe over there, and just wondering based on what he heard from the FDA whether he sees any opportunities for harmonization, which his the second issue that we are talking about today, vis-•-vis what he has heard today.

DR. McCORMACK: I think that industry uses us quite a bit in that most of the clotting factors have been designated if you take a look on our list of designations. Yet given the number that have made it out, I think that, you know, they get it because it is something, but it is not enough.

DR. JAIN: I could speak to the approval process, and as far as I am aware we have seen -- and Toby, direct me if I am wrong -- about accelerated products that we deal with, but we have seen quite a few priority review requests, and we have fulfilled almost all of them.

DR. LACHENBRUCH: Perhaps it is worthwhile to distinguish between accelerated approval and priority review, because the priority review basically says we are going to review this in six months. Whereas accelerated approval means we are approving it on the basis of a surrogate and usually when that happens it will also be a priority review. I don’t think I can think of any cases in which it didn’t

happen.

MR. : I would just like to follow on to Toby Silverman's remarks about registries, and I would say one thing that needs to be kept in mind when you design a registry it would be extremely helpful to be able to capture the basal or natural history of a disease. Because if you have a very varied and variable phenotype and particularly in bleeding disorders, it is hard to know if you have let's say a presentation of data that says this product works in X percent, you don't know if that is what was going to happen in the course of the natural history, and it is actually surprising that anybody with experience in hemophilia will know sometimes people get away with amazing things without coverage or treatment not knowing better or not having ability to treat. I have seen patients who open their hands with chainsaws with hemophilia and actually made it without treatment and showed up a day or two later and everything looks fine. So I think when you design registries you have to take into account it would be very helpful to capture the natural history of treated or untreated with whatever you want to compare your product to.

DR. SEITZ: I would like to answer to Donna whether I -- what did you say, I see some perspectives of further harmonization, and if you ask me that way of course I see these perspectives and that is why I am here. I appreciate

it very much that you invited me as a European regulator, and I think we have very interesting thoughts today and very good thoughts. For instance what you call accelerated licensing is now a new element of the European regulation, same as conditional licensing. You said this was the old name in the USA and it is essentially very similar as far as I understood, and I think also the thoughts about using small patient samples were very interesting. As I told you, there is a new European guideline out for ---, and I would ask you urgently to have a look on that and give your input to that. This would also be a very important piece of further harmonization.

Maybe one difference still, you told us about licensing antithrombin with a small number of 13 patients. We got this for prophylaxis in pregnancy, and there was -- fortunately there was no thrombosis. My question is what would have happen if there was one thrombosis in 13? These are of course there is a risk for this because in pregnancy there is a thrombotic risk factor anyway in persons with a normal antithrombin level, and so in detail it may be very difficult and maybe that is one of the differences. In Europe we do not like to have preset criteria for acceptance. We first want to see the data and then we try to come to a judgement, and we don’t like to be tied as regulators from the beginning with certain predefined criteria.

Maybe that is a difference between us. For instance, we had a case with recombinant factor IX. There was on PTP inhibitor in the safety study, and as you know factor IX inhibitors are rarer than in factor VIII and then a PTP in factor IX, this was really exceptional. Still we thought about it and said, okay, it was a very rare gene defect and there were certain circumstances and, okay. Then we licensed it with a proposal for a post-marketing program, and so far it was not a problem.

DR. GOLDSMITH: I think Keith.

MR. : I wanted to ask Dr. McCormack in terms of for the very, very rare themes, is there a potential for bundling the benefits of the Orphan Drug Act? You alluded to like the $1-million over three years for presumably if an investigator holds an IND for an academic institution. Can that be joint ventured with a tax credit from pharmaceuticals so that you can narrow the distance between say that classified one example used this morning of $7-million of a negative benefit on that drug? If you could leverage several things together you can start narrowing that difference and make it probably more appealing for people to take the risk.

DR. McCORMACK: I think if you were to claim that you spent the $1-million we gave you to the IRS that there would be somebody coming knocking at your door. But certainly any money that -- you know, our grants program

doesn’t preclude anything else. For instance, if you get a grant from a -- typically what happens is a corporation would get a grant from us to develop a product over three years that would be, you know, $1-million. That would probably pay for about 20 percent, you know, in a very small population, probably pay for about 20 percent of the study. They would put up the additional $4- or $5-million to do the study. They certainly could then deduct the $4-million that they put up. There is nothing in there that it is either/or. It all comes as a bundle.

I guess one comment I would like to make since the thing about harmonization came us, and I will probably get some bricks thrown at me when I get back to the agency, but if you ever think about it, why in the world with 200 patients in the whole world would we need to go around to at least four or five regulatory agencies in order to have a therapy approved? You know, this is just such a tremendous waste of resources. Australia and the United States almost had an agreement where we wouldn’t take a common application but we would -- I mean, we wouldn’t take an approval, but what we would do is sort of take a common application and if we met -- for instance, if it was approved in the United States and Australia took a look at it, they would want to make sure that certain manufacturing criteria were met. But they would accept the clinical evaluation and the data as if

they had reviewed it themselves. Now, you know, that is the sort of thing for these very, very rare diseases that makes sense, and I think that, you know, all offices preach for the last 15 years that if there is anything that is going to sort of push modern countries together it has got to be these very rare diseases. Because, you know, that has got to be the first step because it is such an obvious need that you just can't ignore it for too much longer.

DR. GOLDSMITH: Two more comments. Roskia* and then Sandia*.

MS. CARNEY*: I am Roskia Carney* from Michigan State, and I just want to know if as an incentive to the pharmaceutical firms to develop these products --- in addition to having an expedited approval, can we even think about expanded approval? For instance, expanding it to acquired disorders, analyzing them separately so at least the pool of patients is expanded so that the pharmaceutical firms have some incentive to develop these products.

Number two, I also have an issue with diagnosis. Being a pediatric hematologist and in the trenches, it is very difficult sometimes to make these diagnoses. We don't even think about it in the newborn period. These people bleed. We give them fresh plasmas. Some of them die, and I don't know if there is any way to look at the clinical or the lab diagnosis or expedite diagnosis, have diagnosis on a

smaller sample, so I would love to hear your comments on that.

DR. JAIN: First of all, I think there is a scope of studying the indications so it basically comes from the sponsors and the manufacturers. So if they want to expand the indication from congenital to acquired it is their initiative. But the problem we run into is that the two trials cannot be run mix and match, i.e., the same inclusion criteria for congenital may not be the same for the acquired. So there really have to be two different trials with two different objectives, and analysis and evaluation plans. So they both cannot be mixed and matched, and again they both can be studied. The indications can be expanded, and I think most of them, you know, if I understand the incentive for congenital patient population it is mostly, you know, the trials are very small. They can be done, you know, easily and maybe later on expand on to the acquired ones. Most of the manufacturers do want to start with the congenital one, get the product on the market, and then later on do the acquired one. Now lab diagnosis would basically be the diagnostic part of the disease. Now products for interventions, I don’t know how they can affect that part of it, so it would basically -- I mean, that is a different question all together, and I don’t know whether we can address that here.

DR. GOLDSMITH: Dr. Santus*

DR. SANTUS*: Sandy Santus* from the Alpha One Foundation. Far be it for me to defend industry, but we have kind of danced around the issue of the accelerated approval, and it seems to me that there is a major issue with respect to rare conditions. There has been the usual implication that with the accelerated approval these commitments are made and then they are not kept or there is reticence to keep them and things like that. But in fact, I think the real issue is that it is almost impossible sometimes to keep those commitments because once a product is available for a rare condition where there has been a patient community with great need it is very difficult to execute a trial that involves a well-controlled clinical evaluation of endpoints, especially with respect to the words well-controlled because of the -- you know, the issue being that there is often not a standard therapy to compare to. That is why there has been push to get the drug out, and the potential of doing a placebo controlled trial becomes -- is often obviated by the availability of the marketed drug.

DR. WEISS: If you can actually do a study and show, you know, some type of clinically relevant outcome, that is in my mind always better than going for an accelerated approval type of approach. I mean, I did have an earlier slide that I took out, but one of the common

fallacies is companies do trials and they are actually looking at a clinical outcome and they said, "Oh, this is great. Can we get accelerated approval?" because they don't quite understand what it means. I am like why would you want to do that for God's sake? You have got traditional approval, you don't have this somewhat onerous at times requirement for this post-marketing commitment, and -- you know.

I didn't put it on the slide, but I brought with me all the clips that we sometimes get, and this was from early in June, just a couple of weeks ago -- which I can't see unless I put my glasses on, which I don't want to do at the moment. Basically, you know, it describes this kind of outrage that Congress is having now with -- I don't know which products or which studies these are, but they cite a report and say that of 91 products that were approved -- I think they are primarily in the drugs world -- drugs that were approved with accelerated approval, 40-some, about half of them, the post-marketing commitment was done and the other 40 or so, half of those are still ongoing, and in another half the actual clinical trial has not even been started yet.

Now, you know, I don't know what their database is that they were looking at, but they are using this to say this is just a joke, this is an outrage. You know, FDA isn't taking this seriously, industry isn't taking this seriously.

I think that they are a little bit melodramatic as they tend to be of course with this, because I know that people do take this all seriously. The problem, you know, you have raised this issue, and I can tell you, and I was looking just at the database for the therapeutic biological products that I am involved in overseeing at the moment, where may times we have the post-marketing commitment is actually to conduct a couple of trials in sort of different sort of scenarios.

In some of the cases the actual sponsor is relieved of at least maybe one of the commitments because this is in the oncology setting in particular where standards change. You are asked to do a trial in like second-line or first-line therapy comparing a certain combination of drugs and the standard of care changes and it is no longer a relevant question to ask. I don’t know how much and to what extent that is an issue in these rare plasma protein disorders, but I think to the extent that one can look either something that is clinical relevant or develop a body of evidence to show that a particular surrogate outcome is acceptable for an outright approval, you know, that is a much easier road to go down than to try to come up with a reasonably likely surrogate and then try to confirm that post-marketing.

The case that you will hear tomorrow from Alison Lawton from Genzyme I think is particular illustrative of that. It is a similar situation, a rare enzyme deficiency

disorder. The surrogate that was used that was considered to be reasonably likely, engendered lots and lots of discussion about how and what you would do for a confirmatory trial, and she will give -- I mean, I just saw her slides, and she really illustrates a lot of those points that you bring up. I am not sure I have easy answers, because they do raise lots of questions and it does make it very, very difficult. So to the extent that one can actually look at something that has some clinical consequences and clinical outcome, that is a much better scenario to go down.

DR. GOLDSMITH: I think Dr. Walton wanted to say something. Is that right? No? Okay. All right. I think we are at the end of this session then. Thanks to all the panelists and to the audience for your great questions and participation, and we have a 15-minute break, 1-5.

DR. LACHENBRUCH: John, one quick statement. Dr. Ng has shown up. He is right in the back. So just to show that he in fact does exist.

(Whereupon, a short break was taken.)

DR. GOLDSMITH: Let’s get started again. I have one announcement for all the speakers for today and tomorrow. Would all the speakers please assemble in the front of the conference room at the end of today’s proceedings. Mark has some instructions for you. So all the speakers from today and tomorrow please assemble in the front of the auditorium

after today's session is over. Thank you.

Research Support

Jonathan Goldsmith, MD, Session Chair

DR. GOLDSMITH: Okay. Now we are going to continue on Research Support. Dr. Link from the NHLBI is going to talk about NHLBI research support for rare plasma protein disorders, and with no more than that, Dr. Link, please.

NHLBI Research Support for Rare Plasma Protein Disorders

Rebecca Link, PhD

DR. LINK: Thank you. I am glad to have this opportunity to talk about NHLBI research support.

(Slide.)

Research is needed to improve the understanding and increase therapeutic options for rare plasma protein disorders, and research is the area that NIH has and will continue to play a role.

(Slide.)

The National Heart, Lung and Blood Institute in the extramural programs support research related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung and blood diseases and sleep disorders. Now the type of research that is supported ranges from basic and clinical investigations to small business and development, research and development.

(Slide.)

The Division of Blood Diseases and Resources within the National Heart, Lung, and Blood Institute, I have listed here several of the areas of scientific interest and you can see that many of these related to the rare plasma protein disorders. Thrombosis and hemostasis, also transfusion medicine which is involved with blood product safety, and potentially in the future stem cell transplantation.

(Slide.)

Now I am with the Thrombosis and Hemostasis Scientific Research Group, and again I have listed several of our research interests. You can see that these in our research interests is included the areas of rare plasma protein disorders.

(Slide.)

We have heard today and we will probably hear tomorrow more of these deficiencies. They are in the areas of coagulation factor deficiencies, anticoagulation factor deficiencies, and deficiencies in the fibrinolytic system. Again, these are all areas of interest to the Thrombosis and Hemostasis Group in NHLBI.

(Slide.)

Now these are some examples of research that we do support. In the biochemistry of normal and abnormal coagulation factors, mechanism and regulation of fibrinolysis, development of new diagnostic tools,

development of novel hemostatic, anticoagulant and fibrinolytic agents.

(Slide.)

Research that has been supported by NHLBI has lead to development of products such as the recombinant factor VIII and factor IX and recombinant factor VIIa, recombinant activated protein C. It has also helped to improve the blood product safety and identify many of the genetic mutations in these rare diseases. We have also worked at developing animal models, and in particular mouse models for many of the plasma protein deficiencies. These are valuable tools supported by basic research.

(Slide.)

Now the NHLBI can be divided -- the research can be divided into two basic areas, investigator-initiated programs and institute-initiated programs. I want to talk a little bit about the investigator-initiated programs because I will be focusing the rest of this on institute investigative programs. But probably about 70 percent of what we support in the extramural program is investigator-initiated.

Now I gave you a little idea of some of the areas of interest in the last few slides, and these are the areas in which we would accept applications from investigators either utilizing the RO1 mechanism, which is generally an individual basic or clinical project from a single

investigator or institution. These are submitted at regular submission dates, standard submission dates, and they are reviewed by the Center of Scientific Review. We also have program project grants at NHLBI, and this is a collaboration of three or more investigators on projects focused on a biomedical theme or research question. They get a tailored review by the NHLBI. Now in the investigator-initiated programs there is a special requirement at NIH and NHLBI if you request funds of over $500,000 in any one year, and that basically means you need to get the acceptance of the institute prior before you submit that. But again, the majority of what we do is investigator-initiated, and clearly we have interest in the areas of the rare plasma protein disorders and we would be interested in accepting applications in this area.

Now we also have institute-initiated programs, and these fall into two categories. The requests for applications or RFAs, and a key feature of the RFA is that it has set-aside funds. Now we have a limited number of RFAs and a process in which RFAs are brought forth in the NHLBI. There is a special receipt date and a tailored review for these applications. We also use program announcements. Now when in the program announcements there is not a set-aside of funds, and they use the standard review dates and CSR review; but this is a way of showing special interests and maybe

special programs, and I will give you some examples of special programs with program announcements.

(Slide.)

An example of an RFA is improved therapy for hemophilia and hereditary bleeding disorders. This has set-aside funds beginning in fiscal year 2005, this year. The objective of this to study studies of improved treatment of hemophilia, Von Willebrand's disease, and other hereditary bleeding disorders. So we took into consideration in release of this RFA the rare bleeding disorders in addition to hemophilia. I guess we are using the term very rare bleeding disorders, in addition to hemophilia and Von Willebrand's disease. This is actually a collaboration between the NHLBI and the National Hemophilia Foundation. The applications have been received and reviewed, and we anticipate making awards in September of 2005.

(Slide.)

Another program is a program announcement, and this is an example of where we have a special program. In general, NHLBI does not accept applications in what we call the R21, the small grant or exploratory development grant research, but in the area of rare diseases we have put out this program announcement that we will accept applications. Now this is for novel approaches to understanding, treating, and preventing rare diseases. These are feasibility studies,

so the objective is for up to $275,000 to be distributed over two years. Less preliminary data is needed for a R21 application. They do come in at the standard receipt date, which is February 1, June 1, and October 1, and they are reviewed by the Center of Scientific Review. For this and for others I have the link to additional information and you have that on your handouts, so if anybody wants additional information on these programs.

(Slide.)

Now I want to spend some time talking about the small business program, and this -- because I think this is a program that could be utilized by this group very well, and there are two basic programs here. It is the Small Business Innovative Research or SBIR program, and the Small Business Technology Transfer program, STTR program. Again, I list the websites for NIH. I think the first one is for NHBLI, then for NIH general information, and the last one is on a special program announcement that we will have, competitive continuations, which I will talk about in a little while.

(Slide.)

Now the SBIR program actually is an RFA program, but it is an NIH-wide program. There is a set-aside of funds; 2.5 percent of the agency’s budget is for small business research and development. The objective here is to stimulate technology innovation and to meet federal research

and development needs. The objective is to increase the private sector commercialization of innovative research. Now this program has been extended to 2008. The small business, the SBIR program, needs to be submitted by a small business, and so it is the small business and a member of that company needs to be the principal investigator.

(Slide.)

There is a second program, which is he Small Business Technology Transfer program, or the STTR, which is for collaborations between research institutions and small businesses, and there is a set-aside of 0.3 percent of the agency's budget for this. This is to stimulate scientific and technology innovation, and it is to foster technology transfer between the research institutions to the small business. So this is also a program to help support research that was developed through the RO1 mechanism into the small business for further development actually into products. This has been extended to 2010.

(Slide.)

Now both of these programs have a three-phase system. Excuse me. I know I am breaking the rules a little bit here, but I needed some water. Now the phase systems are very different from what the FDA calls the phase I, phase II, phase III, but we are using the same terms, so please don't get them confused. The phase I is a feasibility study, and

this is under the SBIR program for $100,000 for six months, in the STTR program it is $100,000 for 12 months, and the phase I is really supposed to be just a short-time feasibility study so you can demonstrate that you will achieve your goals.

Now the phase II -- and all of these are you submit an application that goes into competition for review. There are special study sections for the SBIR grants. In a phase II you have completed your goals for the phase I and you have achieved these goals, and that is what you submit for your phase II application along with your full research plan for the phase II program. Now in a phase II program it can be $750,000 a year for two -- each year for two years. So we are not talking about a substantial amount of money for research and development.

(Slide.)

We have recently, and that was one of the links that I provided, expanded this to a phase II competing continuation, and this is for research to assess and improve product or device, conduct preclinical or clinical studies, and studies to support a pre-market approval. Now to submit an application for a phase II competing continuation you need to have met your goals in the phase I and phase II. You cannot come in at any point. You have to go through the whole process of a phase I, a phase II, and then a competing

continuation of a phase II; and you need to begin discussions with the FDA, because what we are looking for here is to use this phase II competing continuation to meet your preclinical or early clinical phase studies. It can be up to $1-million a year for three years, so again we are talking about a substantial amount of money to bring some new products to market.

The phase II is the phase now in which there is no longer government funds. This is the commercialization phase, and during the process of preparing your applications you should be looking for someone to collaborate with for commercialization of the product. This is potentially where some of the larger industries could come into play for future commercialization of products that have been developed through the SBIR system.

(Slide.)

Now, another program I wanted to mention is the bioengineering research programs. Many products that come to market will require a bioengineering component, and just as we have in the SBIR program in this under program announcements -- these are now program announcements -- we have different phases that can be supported. There is the exploratory and development or the R21 mechanism again for feasibility studies. There is the bioengineering grants and the bioengineering research partnerships.

(Slide.)

For the exploratory, again this is one of the rare times that NHLBI will accept an R21 grant, and this is for innovative, high-risk, high-impact, bioengineering research. Again, these are feasibility studies, so you do not need as much preliminary data. They have standard receipt dates, and it is for $250,000 distribute over a two-year period. Again, the link is available on the slide.

(Slide.)

There is also bioengineering research grants to apply basic bioengineering design-directed or hypothesis-driven research to an important biomedical area. This is a single or small groups of researchers. It has the standard receipt dates.

(Slide.)

The third is a large program, and this is the Bioengineering Research Partnerships program, and one of the main focuses of this is the development of a multi-disciplinary partnership that would include bioengineering science in combination with biomedical or clinical components. It is for basic, applied, and translational bioengineering research that addresses important biological or medical research problems. Now this program has special application receipt dates. I have listed the next three, and you can request up to $2-million a year for five years. So

this is another program that has been and can be used to accomplish some of the bioengineering questions or problems and get a product to market. Again, I have the website available.

(Slide.)

As you see, NHLBI supports research from early stages of feasibility studies to research and development and clinical trials. The small business and the bioengineering programs can provide a substantial level of support for the development of new diagnostics and therapeutic agents. I have provide here on the last slide my contact information, and my colleagues and I would be happy to talk to anyone who is interested in finding out more about NHLBI support.

(Applause.)

DR. GOLDSMITH: I am sorry. There is one question I think from somebody we can't turn down, Jerry. Dr. Link, maybe you can answer it back up there. Dr. Holmberg is going to ask a question.

DR. HOLMBERG: Dr. Link, I was just very curious about the small business. Is this restricted only to US companies?

DR. LINK: Yes.

DR. HOLMBERG: And what about the bioengineering, could a university apply for this?

DR. LINK: For the bioengineering it is supposed to

be a collaboration, and it can be universities, yes.

DR. HOLMBERG: Once again, is the bioengineering restricted only to US?

DR. LINK: I would have to check that. The major -- the principal investigator, the institution that is requesting needs to be in the US, but there can be foreign collaborators.

DR. GOLDSMITH: Okay. I think we will move along to the next speaker. This is Dr. Garrett Bergman who is the Vice President of Research and Development for Octagen Corporation, and he is going to talk about a small business innovative research grant program for development -- I guess it is OBI-1, is that right? Recombinant porcine factor VIII. Garrett, please.

Small Business Innovative Research Grant Program: Development of OBI-1 (Recombinant Porcine FVIII)

Garrett E. Bergman, MD

DR. BERGMAN: Thank you, Dr. Goldsmith, and thank you, Dr. Weinstein, for inviting me. Yes, the name of the product that we are using right now is OBI-1 and it stands for the companies that are collaborating on this, Octagen and Beaufour-Ipsen as you will see. It has nothing to do with Star Wars.

(Slide.)

Let’s see. A lot of what you are going to see here

you have seen several times before, so there is no better way to learn something than by repetition. What I did here was just make up a table and reiterate some of the things that you have heard before.

Who develops products for rare disorders, I have just put a few of the considerations that a big pharmaceutical company would have in selecting a product that they wanted to develop versus a startup company like Octagen. So the ideal target objective for big pharma would be a blockbuster product, first in class, where the potential market would be over $1-billion. For a startup company, we want to be able to develop a product profitably so that there is a worthwhile return on investment. Period. It doesn't really matter the market size. It depends on how efficiently we can do the job.

The ownership of big pharma generally is publicly owned and they have a big R&D budget, whereas for a startup company it is privately owned and there may be angel investors or private investors. The in-house depth and breadth of the personnel involved, generally in a big pharmaceutical company they have all the disciplines necessary for the complete development of a new product and all of the ancillary supports. Whereas in a small company they may have only selected disciplines and may contract or out-source or share the resources that they need to do the

complete job with their collaborators or with contract agencies.

Presence in the target market, the big pharmaceutical company generally already has or will create during the course of development of the product their presence in the marketplace so that upon approval they are out of the door running as they say. Whereas a small startup company may not market the product at all. Octagen for example is a development company. We are not going to market. We are going to find another channel for distribution, in this case our collaborator.

The level of scientific rigor that has to be maintained, obviously in big pharma we expect them to maintain a high level of scientific rigor and have a proven success record because they have gotten products approved. For a small startup company it is often unknown. It varies. However, to be successful, it has to have high scientific rigor.

(Slide.)

So which company develops products for rare disorders? Answer: any company can develop such a product so long as they can do it efficiently for the amount of money that is justified for the potential market size, and you have heard this this morning repeatedly. The potential market size may not support investment of time and money needed to

develop a product, and you need to add onto that opportunity costs if the company doesn't want to develop this particular product because they would make more money if they developed another product. However, a collaboration among the pharmaceutical company, the FDA, and the NIH through its SBIR grants will permit a small company to develop a new product for a rare disorder that otherwise would not be possible.

(Slide.)

So small company, small market, we are developing a niche product, but as I said the development could be successful only if we can do it efficiently with a clear developmental path and quick decision-making. The expertise of the involved personnel obviously is necessary to do this, people with experience. But also prompt, frequent, and efficient and effective interactions with the FDA are essential for success. We need to understand completely what is expected and how to achieve it because we can't afford time or money to do a study over again, we can't afford lengthy delays for any reason, and we must ask and answer all the correct questions the first time around.

(Slide.)

So Octagen Corporation is a small, privately-owned drug company based in the suburb of Philadelphia. I think a three-person company is about as small as you can get a pharmaceutical company. Founded in 1997, it is based on

factor VIII technology derived from and licensed from Pete Lollar at Emory University. We are now collaborating with Ipsen, a company that manufactured and marketed porcine plasma-derived factor VIII product called HYATE-C. Ipsen is now committed to manufacturing and supplying OBI-1 for the clinical trials and eventually for marketing. The objective of putting Octagen together was to develop this recombinant porcine factor VIII product as a product to control bleeding episodes in patients with inhibitors to clotting factor VIII.

(Slide.)

Need for OBI-1 in the market. Congenital hemophilia, there are about seven to 10 percent of people with congenital hemophilia who have inhibitors at any given time, or maybe that is about 2,000 patients max in the United States. They would require treatment alternative to human factor VIII, which they couldn’t take. They would neutralize it. Acquired hemophilia is a much smaller disorder. The incidence is estimated to be between 400 and 500 new patients a year. The mortality rate is still significant; the last publications I have read still in the range of about 15 to 210 percent. Fortunately it is self-limiting in most cases and most patients will recover within a year or so.

Currently there are available products and they are effective, but not 100 percent of the time, and some people are now suggesting that the two products that are available

be used alternatively so that you don’t give too much of either of them, but they seem to work by different mechanisms to bypass the inhibitor to factor VIII. HYATE-C, the porcine plasma-derived product, is no longer available. It is not being manufactured any longer. There is no blood test for surrogate monitoring of recombinant VIIa or FEIBA for efficacy. It is just clinical outcome that helps you determine whether the treatment is effective, but for a product like OBI-1, recombinant porcine factor VIII, you can measure factor VIII levels in the blood to at least let you know whether you have achieved the desired goal of a level of circulating factor VIII. Based on preclinical studies and very preliminary studies in humans, we think that the dosing of OBI-1 is likely to be less frequent than the alternative treatments.

(Slide.)

Now developing a product for this particular rare disorder, patients with inhibitor to human factor VIII, can be difficult because it can take longer to identify and recruit factor VIII inhibitor patients for the clinical trials. We have heard this from other speakers today as well. Patients with congenital hemophilia and inhibitors often have found a regimen of care that works for them. They self-administer and home care, and when they are offered the opportunity to come into the hemophilia center for

observation of their treatment episodes interrupt their routine, their work in many cases, and spend several days for the necessary testing, they often decline because of the inconvenience. They are currently in a very stable situation. But we do know where the patients are for the most part because the specialty physicians know their chronically-ill, long-term patients very well because most of them in the United States are registered at one of the hemophilia treatment centers. Patients who develop acquired hemophilia, acquired inhibitors to factor VIII, often are referred into the same centers of excellence because the management of inhibitor patients and bleeding in them is well-known by these specialists.

(Slide.)

So Octagen Corporation, we have in-house expertise in clinical development, both of us, and including development of previous hemophilia products. We are collaborating with Beaufour-Ipsen, known as Ipsen now. They are an established pharmaceutical company based in France, long commitment to hemophilia with their product HYATE-C, the porcine factor VIII product. They are providing regulatory affairs function for us and the entire manufacturing team to insure that the CMC section is of high quality sufficient to meet the requirements. Their commitment to our program is evidenced by the fact that they have just built an entire new

factory in Medford, Massachusetts, dedicated to recombinant products, of which OBI-1 is the first that they will manufacture there, but they hope not the last.

(Slide.)

The SBIR grant support that has come from the NIH has permitted the development of this product to continue past the time when your classical return on investment calculations might otherwise limit or preclude further investment in the program by investors. One of our investors tells me that he allegedly uses a discount rate of about 35 percent, so you can see that any delay that we would get would immediately say this is not a good investment for him, but every program seems to incur delays. As a matter of fact, when we started out by the middle of 2005 we thought we would be filing our BLA, and here we are in the midst of just starting up a phase II program. So the grant from the SBIR program clearly shows the NIH commitment to new products for rare plasma disorders that might otherwise be impossible to develop. In some ways this has been suggested in the discussions as a very good collaboration between NIH and other companies to accomplish this goal.

(Slide.)

Octagen has been the recipient of a phase I SBIR grant and a phase II SBIR grant as Dr. Link has just described, and we want to specifically extend thanks to the

NHLBI for the confidence that they have shown in our program and the support they have provided. We have also applied for the phase II continuation grant, which decisions have not yet been made on that. We anticipate the funding that we have had so far in the phase I and phase II will take us far toward completing of OBI-1, and we expect that at the end this program will be one that the NIH through its SBIR program will be able to point to with pride in demonstrating their support for a new product option for patients with this disorder. Thanks.

(Applause.)

DR. GOLDSMITH: Questions for Dr. Bergman? Okay. Why don't we proceed to the last speaker of the day.

Reimbursement

_____DR. GOLDSMITH: This is James Bowman, Medical Director, Chronic Health Care of CMS. He is going to talk about Medicare payment for drugs and biologics. I see him in the back.

(Adjusting equipment.)

Medicare Payment for Drugs and Biologics

James Bowman, III, MD

DR. BOWMAN: Good afternoon. Thank you for saving the most exciting topic for the end of the day.

(Laughter.)

In the interest of time and also content I may

deviate just a little bit from the slides to make it a little more relevant to what we are talking about. There will be a lot of regulatory and statutory gibberish that may appear on the slides, and it is not really necessary to memorize and learn all that. It is just there primarily for reference and background purposes.

(Slide.)

Just in the next few minutes I am going to try to go over very briefly sort of the framework and environment or contacts in which CMS actually administers and makes payments for the biologics and drugs for the Medicare program, in particular relevance for this particular program today and tomorrow. I will cover some of the statutory constraints, some of the legislation constraints that they work within, and in particular the particular relevant changes in payment of drugs and biologics that were introduced by the Medicare Modernization Act about a year-and-a-half ago. One of the biggest changes of course is the average sales price method of payment, both in the physician office setting and a very similar design within the hospital outpatient department for biologics and drugs, and also very briefly IVIG home benefit under the new legislation.

(Slide.)

So to step back just a minute, the Medicare program itself is really divided into three large payment systems, if

you will. The Part A system pays for all the inpatient care primarily. Now the physician fee schedule under Part B covers the physician professional services, even for the inpatients, which the clinicians here obviously are aware. Hopefully they are getting paid, but the Part A program really pays for all the inpatient. The Part B program pays for a whole host of what we might consider just about everything else with one notable exception, which is outpatient oral prescription drugs up until very recently.

The Part C program is the managed care version of Medicare. There are about five-million members nationwide still in some managed care plans, and actually this trend is increasing with the new legislation. There are some incentives with the new legislation to encourage beneficiaries to enroll, and this is now called Medicare Advantage. It used to be called Medicare Choice.

Then finally the Part D program, which is a very expansive expansion of the benefit under Medicare for beneficiaries which will take place in January, 2006. It is the so-called drug program, which is what you may have heard about in the news over the last year-and-a-half. This is the oral prescription drug program that supplements essentially the benefit for drugs that are not currently covered under both the Part A and Part B and Part C programs. Any oral drugs that are administered while a patient is in the

hospital are of course covered by the hospital payment and oral drugs that are administered in the outpatient department of hospital clinics as part of the treatment in that setting would be covered there. But by and large, with some notable exceptions, oral drugs are not covered currently under the Medicare program except for the drug card which went into effect last year for a very time-limited program under the MMA as it is called.

So that is a very expansive benefit. What it does not do though, for instance to give you an example, immuno-suppressive medications are covered under the current existing Medicare program and they are accompanied by some deductibles and co-insurance that the beneficiary has to pay. So it can be expensive for those patients, and the Part D program will not be a -- like a supplement or fill in the gap sort of for that kind of oral medication. Those are still covered under the existing Medicare program. So the Part D program will pick up oral prescription drugs that the current so-called traditional Medicare program does not cover.

(Slide.)

I think I covered some of this, but just amplify. Most of you are aware that the inpatient payments are made through the DRG mechanisms. Those have been adopted obviously by the Medicaid programs in the states and also by a lot of the commercial third-party payers. Not necessarily

with the exact same amounts, sometimes less and sometimes more than the Medicare program. Unlike third-party commercial payers, however, the legislative constraints for payment in the outpatient hospital setting is quite different. It requires a DRG-like payment system similar to DRGs for inpatients, but is called APC, which is an acronym for ambulatory payment classification groups in the outpatient system. By and large, these are little bundled groups. There are quite a few of them that accommodate all the facility services that are rendered by the outpatient department of the hospital.

There are some exceptions in the sense that if a drug or biologic costs more than $50, which is the threshold limit set by statute for 2005, 2006, then that drug or biologic is assigned to separate APC payment in addition to whatever other services are rendered in the outpatient hospital clinic. The physician office setting, on the other hand, is quite different. It is paid for through the physician fee schedule, again under Part B, and that covers all the physician’s professional services done in outpatient setting whether it is done in the outpatient hospital department, such as a hospital outpatient surgery center, or even in the physician’s office in a surgery center in the office. It also covers drugs that are administered in the office setting that are otherwise not -- cannot be self-

administered.

Finally, there is a new benefit under the MMA called the home infusion benefit for primary immune deficiency disorders for intravenous immunoglobulin I am sure many of you are aware of. This is payable under Part D for the beneficiary. Unfortunately the way the statute was constructed it did not cover any durable medical equipment expenses that the beneficiary might incur, nor did it cover the ancillary staff services such as nursing or home health staffing that the beneficiary would incur. So this can lead to some considerable extra expenses on the part of the beneficiary, and furthermore under the Part B program in particular there is a 20-percent co-insurance requirement that the beneficiaries have to pay after a certain deductible that is met each year. As you are well aware, some of the --- can get quite costly, and so 20 percent would be quite a lot for most of us in this country.

(Slide.)

The reason I set the stage for all this is to show how the payment for any one particular item, whether it is biologic or drug, under the Medicare program depends a lot on where that particular drug or biologic is infused or administered in terms of what setting. Whether it is in the inpatient setting, whether it is in the outpatient department hospital setting, or a hospital clinic if you will, or

whether it is in physician office setting, and of course in the intravenous immunoglobulin home health setting. These particular payment constraints, if you will, or payment systems, pretty much dictate by statute what Medicare program is allowed to pay and the methodology that the CMS must use to pay for these agents. Then what follows on from this obviously as most of you are aware is that depending on where a patient gets his or her treatment or product will likely differ for each setting. Even though it would be ideal that the payment would be sort of -- would not be site specific or site neutral, that is not often what occurs under the Medicare program, and this is the reason for that.

Just a couple of notes in terms of this particular slide. Where it says under the HOPPS, that is an acronym that we use at CMS for hospital outpatient prospective payment system, and that is the DRG kind of program for the outpatient department. It says MMA for plasma and drugs. That means it is specified by the MMA for 2004, 2005, and then 2006 and beyond. In particular, the plasma-derived products are considered sole source for the MMA purposes for outpatient hospital departments. Again, there are some specific payment that is set by the MMA for clotting factors. Then finally, the very far right lower corner under physician office setting, clotting factors are paid under a system that I will talk about in just a minute called average sales price

plus six percent. But in addition specified again by the MMA statute, a $.14 per unit furnishing fee is added onto that, and that $.14 was based as result of an initial proposed $.05 per unit last year and then based on comments from providers and patient advocacy groups and some research organizations that number was adjusted upward to $.14 per unit. This payment of ASP plus six percent plus $.14 per unit would be adjusted in the future based on consumer price index, and that is again by statute.

(Slide.)

I am not going to spend a whole lot of time on this slide. I just wanted you to know why in the hospital outpatient department for those of you who do work in the hospital clinics, the payments come back sometimes the way they do and they look a lot different for drugs and biologics than they do for the physician office setting. Multi-source innovator and sole source are distinguishing terms that are used specifically in the statute and sole source is generally a brand drug and multi-source innovator is a multi-brand drug, and then the multi-source non-innovator is the generic drug. In the future, the OPPS, outpatient payments, are going to be based largely on what is reported the GAO survey, and then there are going to be a lot of drugs and biologics that the GAO survey is not going to identify. In that case, the CMS is going to have to interpellate and use a reasonable

method as a proxy, and what they are going to use probably is ASP plus a X percent, which hasn't been set yet. The proposal will be out later this summer for the hospital outpatient department payment system, and then hopefully in that it will be fairly clear what they are proposing for payment in 2006.

(Slide.)

This is just some regulatory gobbledygook that provides the background reference for sole source and multi-source innovators and non-innovators.

(Slide.)

There are a couple of exceptions under the hospital outpatient department payment for drugs, and those are listed. But in particular, the orphan drugs for 2004, 2005, are -- the payment rates are listed as you see there. 2006 will be based again pending the proposed ruling that comes out. I think I have got the next slide to show --.

(Slide.)

I jumped on to the physician payments, but the statute is fairly sparse in the way it describes how CMS needs to identify payment for orphan drugs. So I will point out that is one opportunity during the comment periods during the hospital outpatient payment system that it is probably worthwhile to look at those proposed rules when they come out and comment appropriately as you see fit. There is some

discretion involved compared to some of the other types of services and products that CMS sets payment policy for.

The physician drug payment system is probably the most sweeping changes. Up until this year physicians were paid primarily at 95 percent of AWP for most of their infused drugs in offices. The MMA changed the Social Security Act sections that were applicable to that payment setting, and there were three parts of the SSA that has changed. One is 1847, which eliminates the 95 percent AWP except for some exceptions. Then 1847A which sets what will be the standard payment methodology going forward from now on until I guess changed again by Congress, and then 1847B is probably more controversial, called the competitive acquisition or also called competitive bidding in the public sector to describe how the methodology is.

I am not going to get into details in the interest of time of the ASP and wholesale acquisition costs. I will just say the wholesale acquisition costs is an alternative backup in case there isn’t adequate data from the manufacturers, the drug and biologic manufacturers, to set ASP rates. Primarily the ASP method is a way of volume weighting all the reported prices of the drugs or biologics that the pharmaceutical or biologic manufacturers supply to CMS every quarter, and then six percent is added to that. That is a six percent number that is fixed in the statute.

That is not the same number as a physician, he or she, may have to pay an invoice to obtain a particular drug or biologic. It is what the manufacturer is stating that they have made sales from their factory.

(Slide.)

There are special payments under the ASP for single source drugs, and they are defined as either a biologic or a drug that is not a multi-source drug and that is specified in the statute.

(Slide.)

There are some exceptions to the ASP method for paying physicians. Blood and blood products is a notable exception, also vaccines like pneumo vacs, hepatitis B, and influenza. Most importantly I think to this program is there are no exceptions made for the orphan drugs, so right now the orphan drugs will be subject to the ASP plus six percent, which is I think worthy of note. When the physician proposed rule comes out, again late -- mid to late summer -- it already feels like mid summer, so think of late summer -- it is worth looking at what may show up on those rules in terms of what they propose for payment for orphan drugs.

(Slide.)

I think I have already discussed the methodology for ASP. Again, it is based on what the manufacturers report to CMS and it is updated quarterly and it is a volume-

weighted average of all the reports. There are going to be some instances where CMS is not going to get reports from certain manufacturers, and the so-called acquisition cost method is an alternative, and that is just based on what the manufacturer reports as a price and not an actual volume of sales.

(Slide.)

Again, the most probably controversial portions for physicians in particular is the competitive acquisition. This is going to begin in January 1st, 2006. It is going to involve a whole group of categories of drugs. I think the salient points about competitive bidding or competitive acquisition is that it is an option for the physician. What happens when the physician elects to take a competitive acquisition or competitive bidding payment is he or she does not actually buy the drug and then so-call resell it or furnish it to the patient and collect from the patient and then submit to Medicare for reimbursement. What the physician will do is be totally removed, if you will, from the paperwork process of that and a supplier who will actually have to bid on different geographic areas of the country for different competitive drugs will actually submit the bill to Medicare. So it takes the physician out of the loop so to speak, but it also -- there are some down sides to that because the physician has certain leniencies you might

say and discretions when he or she provides a certain drug in the office setting and then gets ASP plus six percent. The only problem with ASP plus six percent is, as many of you know, it may not always cover actually what the invoice to the physician is when he or she purchases that drug depending on what an intermediary or intermediary supplier happens to charge for that drug or biologic.

Again there are a couple of notable provisions for exceptions to the competitive acquisition program when it begins. These are based on the Secretary's determination that there are either no significant savings or potential savings to the Medicare program, in which case it would be silly to even implement a competitive acquisition for that category of drugs, or on the other hand if there is an adverse impact of access to particular necessary products for the beneficiaries. That is another criteria for an exception to be excluded from competitive acquisition.

(Slide.)

I have already discussed IVIG home infusions, so I think I will again dispense with that in the interest of time.

(Slide.)

And I will also dispense with this. Most of you all are familiar that the CMS broke out the two IVIG HCPCS codes by specifying lyophilized and the liquid formulations

earlier this year.

(Slide.)

Finally, in your handout there are some website references that go into a lot more detail that might help answer some of the questions that come up. I also have listed my contact information, in which case I don't know all the answers obviously, but there are a lot of smarter and wiser people at CMS that I can put you in contact with who are quite adept at a lot of the issues that we have talked about.

I think that the take-home that I would like to leave with you, the two take-homes, number one is that CMS right now is tasked with trying to cut corners or save costs or save money. Administratively within, you know, the facilities and the staffing and things like that CMS has to be obviously prudent just like all departments and agencies within the federal government. But in terms of administering the Medicare program CMS pretty much has a statute construct that is handed to them by Congress, and they are basically charged with paying in accordance with that statute. Sometimes there are ways that sometimes some of us might see that it could save money, but again unlike when I used to work with third-party payers, we are not tasked with that and we are pretty much tasked with obeying the statute and the laws the way they are written.

The other thing I would like to leave with you is that even in instances where it seems pretty clear cut and black and white, certainly in those instances in the regulatory relations and statutes where there is discretion or if there are less-than-detailed prescriptions in the statutes, then CMS has to do its best, make its best effort, to try to come up with fair and equitable ways to provide payments and reimbursement. But that doesn't mean it is cast in stone, especially when the proposed rules come out each year for the physician and outpatient department and even the inpatient payment rules. So it is worth considering to submit your comments, because they do -- I can vouch that they do look at every comment when it is submitted, and they are tasked with responding appropriately to those comments. So I think I will stop here, and I will hang around if any of you have any questions afterwards.

(Applause.)

Open Panel Discussion of Research Support and Reimbursement

Amy Shapiro, MD, Session Chair

DR. GOLDSMITH: Okay. This is the last panel today and the last event of the day. If I remember what Mark said we have to leave by 5:30, right, from the conference hall? Amy Shapiro from Indiana is going to be the -- no, no, you have the expertise -- is going to direct this panel discussion. So three speakers from this afternoon.

DR. SHAPIRO: Thank you, Dr. Goldsmith. Nice to see you. That is all right. I would rather be standing. I have been sitting too long. Well, I would like to open up the last session today for discussion. I think we have heard some interesting information about some opportunities for funding from NIH and a nice story about how that has actually been utilized in the real world for development of a product, and then a somewhat confusing discussion --

(Laughter.)

DR. SHAPIRO: -- on Medicare rules which I think will take some time to figure out exactly what you said, but I am sure it was important. So does anyone from the audience have any -- yes, Mark.

DR. WEINSTEIN: This question is for Dr. Bowman. Jim, my understanding or my recollection is that how the FDA defines blood products and plasma products is different than how Medicare does or that CMS does and that there isn’t complete harmony between the two. I guess what I am wondering is when companies are looking at developing products to treat rare disorders, is there a way for them to come in and meet with you prospectively? And in the absence of other treatments that exist, then they would be looking at --- as the typical payment mechanism, or how can they get a sense of what the reimbursement will be? What we heard in the first discussion today is they need to know they are

going to get paid or can get a payment for the products if they are going to develop them, and can you tell them that prospectively when they are just sitting there at their lab bench trying to decide whether to make it or not?

DR. BOWMAN: Sure, Mark. Thanks. That is an important question. I appreciate that because it is a little confusion even for those of us in CMS obviously. In terms of whether they will get paid or not, I can answer that much. Yes, they will get paid by and large as long as there is coverage. We didn't even address coverage today, but that is a whole separate issues within CMS is whether something is going to be covered or not in terms of eligible for being paid in the first place, but by and large -- I was going to say except for drugs like Viagra, but I better not go there because there are some issues about that also. For the most part, CMS does pay under the Medicare program for the drugs and biologics. I think -- is there a transcript of this or not later?

MS. : Yes. We take that out. Can't we? We can take something out, right? We can take something out?

(Laughter.)

DR. BOWMAN: Well, if you look back and see historically what CMS has considered blood and blood products and what it has considered to be other if you want to call it that, and other of course is other biologics and plasma-

derived therapies which you are familiar with. It is pretty obvious I think, it seems obvious, that the blood and blood products for CMS's purposes -- and you are correct, there is not complete harmonization or congruency between what CMS considers as blood and blood product and what the FDA does. It appears that historically and traditionally it looks like CMS considers blood and blood products something that is used with minimal processing after collection of the blood or plasma or blood component. As opposed to a biologic that is not a blood and blood product which appears to go to some sort of outside facility, goes through extensive processing, somewhat similar to pharmaceutical drugs, and then comes back maybe at a later date to the patient.

In all honesty I don't see that changing in the near future, so to answer the second part of your question about how they would anticipate getting paid and reimbursed under the Medicare program, it probably will be -- at least for the physician setting, it probably will be the ASP plus six percent unless that is changed by Congress at some point, which doesn't look likely this year. It certainly could in the future. As you well know and as I alluded to, the ASP plus six percent may or may not cover all the distribution chain and distribution channel costs that get added in before it finally reaches the patient, and certainly for the physician having to purchase something with an invoice.

The hospital outpatient department is not exactly on the ASP plus six percent system, but it is going to be somewhat similar in that sense. So these are very expensive drugs and biologics that certainly meet the threshold of $50 for their own ambulatory payment classification group under the hospital outpatient payment system, but they are going to be based under the OPPS under claims-based cost to the hospital. So again, a lot will be dictated by what the manufacturer actually charges in the marketplace when the manufacturer sells this product to suppliers and distributors, but it may not always reflect, especially on the physician side, with the ASP plus six percent exactly what the physician has to pay to acquire this.

Again, because of the provisions to exceptions for competitive bidding it is likely that some of these drugs under -- I am sorry, some of these drugs and biologics that are used for the rare plasma protein disorders may not -- may likely be excluded from competitive bidding or competitive acquisition programs. I would not be surprised if that was the case. It seems fairly common sense if you will, but again hopefully they won’t read all the transcript back at the fort.

(Laughter.)

DR. WALTON: I guess I will follow protocol and identify myself. Paul Walton from ZLB Behring. A question

for Dr. Link regarding the small business programs by way of a comment. Thanks very much for the presentation. It was very, very clear. These obviously show a lot of merit for studying -- small businesses in studying innovation. My question pertains to the demonstrated usefulness of these programs for rare diseases, and I was struck almost by that what might be more useful than a small -- what might be useful in parallel to a small business type of grant might be a small indication grant that wouldn't be limited by the size of the business, but would be focused on the small and rare indications. My question is what -- can you share with us your metrics on how many of these grants have been given to small businesses to develop new pharmaceuticals and how many specifically are focusing on truly rare diseases? And a second part of that question is what are your goals. What are your goals by the end of the program to actually continue this program beyond 2008, 2010? What do you have to actually achieve to demonstrate a lot of merit, it is working, we have done all these great things?

DR. LINK: I am afraid I really can't answer most of your questions. I will tell you though that there is now in effect at NIH a mechanism where they are going to try to evaluate program. So that was not incorporated at the beginning of it. However, all the information regarding the number of grants that have been awarded, that type of

information, is available on the NIH website. But in terms of success, that is something that is really being looked at, and they are trying to evaluate it at this time. One of the things I think that is interesting and it comes up annually, I believe the next one will be in July, is a program in which they talk about the SBIR program and they actually have people who have participated come to NIH. That can be a very beneficial program in which you learn more about the SBIR program, but also in which people who have participated can interact with each other and the information of some of the successes.

DR. SHAPIRO: Any other questions? Donna.

DR. DiMICHELE: My question is for Dr. Bowman. I guess can you comment at all on Medicaid and I know you are primarily discussing Medicare, but Medicaid, how they currently treat orphan drugs and what we can anticipate for instance if products for rare bleeding disorders are licensed?

DR. BOWMAN: Yes. My comments will be brief. I honestly don’t know what the oversight parameters are that CMS institutes on the different Medicaid agencies around the states for orphan drugs. I can take that back to them and find out and get back with you if you leave me your contact information afterwards. As you know, there are some broad coverage parameters that CMS by statute institutes for all

the Medicaid programs around the states, but a lot is left to the discretion in terms of payment to those individual states and there have been some very drastic upheavals as you know from the news over the last year or so that the states are going through. So I don't know what impact that has had on orphan drug coverage and whether there are any specific mandatory type constraints or requirements that the Medicare program imposes on the Medicaid agencies around the states, but I will get that to you.

DR. SHAPIRO: If you are going to take something back, could we throw one more thing at you here? As you bring this up, rare disorders are actually being impacted by lack of Medicaid coverage, and it is mostly in the inpatient hospital setting where in many states the hospitals are reimbursed as a DRG without any separate passthrough for whatever payment for drug is being required. So whereas Medicare has acknowledged that this is a problem and has since instituted a passthrough, it hasn't been put into the Medicaid state plan requirements that this also be done for Medicaid recipients, and so they are suffering because of that.

DR. BOWMAN: Yes, I will be happy to get that information for you.

DR. SHAPIRO: Because we would like to change that.

DR. DiMICHELE: Amy, could I follow up with a

followup question?

DR. SHAPIRO: Certainly.

DR. DiMICHELE: It has to do with Medicare, again Dr. Bowman and Medicare. Back to Medicare, with respect to the orphan drug payment schedule currently as it is, say 2005, have you heard about any problems related to, you know, reimbursement for any orphan drugs? I mean, have there been any challenges? And also give the fact that we have heard, you know, industry may have to charge more for orphan drugs, 88 percent of -- I forget what it is -- AWP or ASP plus six percent, may certainly leave these patients with a large co-pay, and is there anything that addresses co-pays or is planned to address co-pays for very expensive drugs?

DR. BOWMAN: Okay. The answer to your first question is have we heard of any problems with access for the orphan drugs or complaints or issues with payment; and, no, we haven't. That doesn't mean there are not issues out there in the field. Often we are one of the last to know about problems as they occur in the field setting. They go through several layers before they get to the central office and often they go through the carriers and intermediaries, the contractors who pay the bills to the physicians and the hospitals. The second part of your question about the --?

DR. DiMICHELE: Relates to co-pay.

DR. BOWMAN: Sure. The current payment right now

is as you said, it is a max of something up to 88 percent of AWP or another and the cap. It was the larger of the two, but no greater than 95 percent of AWP, which is a fairly they thought, or reasonable payment at this time for that. The 20 percent co-pay unfortunately under Part B is a statutory requirement that doesn't affect just the orphan drugs. It actually affects a large number of treatments for Medicare beneficiaries in numerous different kinds of situations, settings. It affects the primary immune deficiency patients in the home setting receiving IVIG. There are oodles of co-payments under the Part B for skilled nursing facility and home healthcare, so --

DR. DiMICHELE: Hemophiliacs.

DR. BOWMAN: Yes, absolutely, and so that is a huge issue that transcends a lot of issues with Medicare beneficiaries that we do not see any relief from, at least right now, until some other legislative act is enacted.

DR. SHAPIRO: One more issue to bring back. You find these little loopholes when you take care of patients that you didn't realize existed, and one of them for Medicare patients is that when they are in long-term care facilities or rehab hospitals their factor concentrate isn't paid there. So it is in the hospital, but you can't get them into a nursing home or rehab place because it is not paid. Yes. That would be nice to fix that inconsistency, not to the

detriment of the inpatients, but to the benefit of the rehab hospitals. Yes?

MS. BAKER: Judith Baker, Los Angeles. A question for Dr. Bowman with respect to the competitive acquisition that will be rolled out in 2006. I was curious about the implications on blood and blood products, so I wondered if you knew if they were excluded, and if not what realms the physician payment would be in. If is just the individual physician offices or the outpatient, and what the parameters are in terms of a physician selecting their payment method.

DR. BOWMAN: Sure. I glossed over that, and I should have made myself more clear. The MMA specifically excluded blood and blood products from any changes in the payment for that particular category, although it instituted a whole host of other changes for everybody and everything else. It left them alone, so it will continue as it currently and was, and maybe every shall be. Who knows?

MR. JACKMAN: May I add to that also? Up here, Dennis Jackman, from ZLB Behring. Just in terms of IVIG was statutorily exempted from the CAT* program of course, and under the pretense of course and under the bases that these are rare disease products, relatively limited amount of product in the marketplace, different distribution systems, et cetera. I would certainly like to see that apply to other plasma therapeutic proteins. It would make sense. It

doesn’t make sense to have one and not the other. So there has been extensive outreach to Congress and to CMS to try to actually broaden that exemption from the CAT* program for all plasma therapeutic proteins.

DR. SHAPIRO: Dr. Hoots.

DR. HOOTS: For Dr. Bowman. It seems like it is prototypic of the American reimbursement system to cost shift, and you have described several scenarios where it seems like it is likely that cost shifting is going to accelerate. One is if in the physician setting the physician or his office or whatever the entity is cannot break even then they will not provide the service. That is just a given. I mean, that is just a fact. Which means that those individual patients will go through emergency centers and back in to Part A. Does CMS have a way to track that to see the implications of the reimbursement on themselves first and foremost, but on the broader society at large? Because it seems only if that is tracked will we really understand before years go by what the implications are except for the hues and cries of physicians and healthcare professionals.

DR. BOWMAN: Well, just briefly, the hues and cries will actually get more attention than just routine surveillance and monitoring of cost and especially drilled-down sort of analytical costs. Now a large bump in any expenditure through the Medicare program will get some

attention and then some sequent analyses and reports to see where the money goes so to speak and follow the money trail if you will. But just judging from the little time that I have been at CMS for the last two years, hues and cries are very worthwhile.

Now having said that, I will say that thanks to actually since CMS does not look at its primary purpose as trying to track cost shifting per se, although it certainly is one of the things that CMS should be doing, sometimes they just seem to be overwhelmed with just trying to obey the law and pay the bills so to speak. But thanks to some of the initial hues and cries that have come out recently, for instance on the IVIG issue with cost shifting --- that will result from physicians being unable obtain IVIG and still get reimbursed to even break even if you will. Dr. Holmberg has taken the initiative and the lead on that both with FDA and with CMS and trying -- and with of course the external stakeholders that are involved with this, and has brought this admirably to the CMS leadership and staff, and they are working through his office to try to track this on a number of different levels -- both through the carriers and --- intermediaries who are our contractors also through the regional offices. There are 10 regional offices around the country, and through the central office and through the patient advocacy groups like the Immune Deficiency Foundation

and PPTA and others.

DR. SHAPIRO: Thank you.

DR. HOLMBERG: If I could just follow up on that. By the way, there is an article in OP today about the IVIG situation and HHS has responded with some comments on that. What you are saying as far as the shifting we have seen with the IVIG and what is critical about this is come January 1st of 2006 the potential -- and I don't know if you were aware of that when the slide went up there, was that the potential is for the IVIG in the hospital outpatient payment system to shift either to the APS plus six or to a GAO survey. In lieu of a survey it will go to the APS plus six. We already know that there has been quite a shift from the physicians' offices to the hospitals, and if it is less than 24 hours it goes under the HOPPS. Okay? So what the next shift might be is to admit them for a longer period of time over the 24 hours into -- under a DRG. So that is what we are trying to look at right now, is what is the cost effectiveness of all of this, and like what Dr. Bowman has mentioned is that our hands are tied on a lot of this because it is Congressional.

You know, it is by statute we are required to do some of this. You know, even to the point of the durable medical equipment that was omitted out of the MMA, you know, we realize that it is wrong. However, our hands are tied, and so whether Congress opens that up or not, the MMA this year,

we don’t know. But we are trying to work the issues, and the thing is, you know, what it is going to cost. I mean if we are really into a cost-savings mechanism we have to do what is right and look at the entire system on that. The thing is that even with the ASP plus six we realize that it is not probably -- well, we know that it is not an effective way in a volatile market. Okay. So if it is a stable market it may be a different situation.

DR. SHAPIRO: Donna.

DR. DiMICHELE: I would like to address my question to Garrett. You know, because I think it is very important. I think your presentation was very important in terms of, you know, somebody who has actually used one of these initiatives, and I happen to know that, you know, in your professional life you have also probably been able to take advantage of some of the other initiatives like orphan drug if I remember and some of the other initiatives. So I was just wondering given your role in industry, you know, over the years, if you can comment on the question that I posed to industry previously about the initiatives that are currently present in the FDA such as orphan drug, the small business grants, a lot of these initiatives to get rare drugs to the market and whether your -- you know, your feeling personally is that, you know, the FDA is doing what it could be doing in terms of getting these products to market and where, you

know, in your opinion we should try to make some changes to make this easier. I don't mean to put you on the spot, but you do have a lot of experience so I want to ask you.

DR. BERGMAN: Yes. I have been involved in a couple of companies where part of the decision to develop a product has been the ability to achieve orphan status for it knowing that changes the formula on the return on investment. That has been very good for companies I have been in, but I also happen to know that the orphan products division of FDA is very proud of how many products have taken advantage of that. As far as SBIR, this is the first time I have really been involved in that process and certainly for developing this product it has been very helpful. I haven't really given much thought to where else they could do -- one of the things that I will say is that particularly in this part, but even in my previous experiences of developing products before, the most helpful thing is the interactions with the reviewers to understand exactly what we can do in developing the product that would answer the questions efficiently, scientifically, rigorously, and the dialogue has been very helpful. That is one area I think that the reviewers that I have been involved with have made a concerted effort to do just that, and it is paying off. It is helping.

DR. SHAPIRO: I think just to follow up on what Donna is saying, though, on the physicians' perspective is

the issue of some of these things that we are talking about have a viable market where you could conceivably get a return on your investment. Some of these diseases may not have a viable market, and I wonder if there is some category that could be created more on the lines of compassionate care for some of these disorders. Just a question. Yes, last question?

MS. BENZINGER: Hi. I'm Anne Marie Benzinger with Alpha One Advocacy Alliance and I am speaking from the patient perspective and I would like to speak to Dr. Bowman. We have grave concerns in the Alpha One patient community about access to these services. We have gotten these wonderful new products be able to come onboard and then restrictions on whether we are going to be able to get them based on the price limits that you have put on them, and this goes to being denied, you know, services and a choice by patients and their doctors making those decisions who is actually, you know, the person who should be making that decision for the patient. The other choice problem I have with CMS at this point and HHS and everybody else making the decisions on it, home infusion is not covered for Alpha One Antitrypsin protection. We as patients can't get this if we are on Medicare unless we are homebound. Yet, it is proven that if we are up and we are active we are much healthier, and if we stay out of a medical facility we stay much

healthier. So the home infusion makes so much sense, and it has the patient up and out and up and moving around, but not going into a dangerous facility that is providing numerous germs. I would like this to go back to the big house.

DR. BOWMAN: I will certainly take those comments about -- and I would like to get more information about that one, antitrypsin issue with the pricing and also the denials if you can provide that afterwards because I am not as familiar with the issues involved with that. You are absolutely correct. Home health, if you will, home health infusions of many medications and biologics make a lot of plain old dollars and cents as well as common sense. It currently is not a benefit obviously except for the IVIG for primary immune deficiency and that is based on again what Congress has handed to CMS at that big house. As you know, many third-party payers do have fairly lenient policies with the use of home infusions. It is definitely a cost-saving measure for them, and there are certainly demonstration projects underway at CMS with demonstration programs to evaluate not only home infusions, but a lot of other practices that third-party commercial payers are using right now to save money, if you will, to provide more cost-effective medicine. But I will be happy to take that back also, but you are probably going to have to take that down the street, you know, at Capital Hill to get that changed.

DR. SHAPIRO: I see Dr. Bowman's sheet is full, so based on that I think I would like to thank everyone for their attention. Mark, do you want to say any closing remarks?

DR. WEINSTEIN: Well, again, I would like to thank all the speakers today. I think it was a very interesting session. We will continue tomorrow bright and sharp and 8:00 in the morning, and I think that we will continue to probably to understand the process of facilitating these new products, bring products for rare plasma protein disorders to the market. I think we will hear -- I know tomorrow we will hear a number of case studies where this is currently underway or has been achieved, and I think that these in particular will be very instructive for all of us. So until tomorrow I look forward to seeing you.

So again, speakers please come down to the front here. I want to give you some further instructions about this evening.

(Whereupon, the meeting was adjourned, to reconvene June 14th, 2005, at 8:00 a.m.)

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KEYNOTE: "---" denotes inaudible in the transcript.
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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.)