Cover Page

I N D E X

***Biological Therapeutics for Rare Plasma Protein Disorders***

***June 13, 2005***



I N D E X (Cont'd.)

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

P R O C E E D I N G S

***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.)