DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

INTRAVENOUS IMMUNE GLOBULINS IN THE 21st CENTURY: PROGRESS AND CHALLENGES IN EFFICACY, SAFETY, AND PATHS TO LICENSURE

Wednesday, April 13, 2005

8:00 a.m.

Lister Hill Auditorium
National Institutes of Health Campus
Bethesda, Maryland

P A R T I C I P A N T S

SPEAKERS:

Paul Aebersold, Ph.D.

Don Baker, Ph.D.,

Mark Ballow, M.D.

Melvin Berger, M.D., Ph.D.

Rebecca Buckley, M.D.

Erwin Gelfand

Basil Golding, M.D.

Jonathan C. Goldsmith, M.D.

Mary Ann Lamb

Hans D. Ochs, M.D.

Judi Miller

Joshua Penrod, JD, LLM, MPH

Joan Robertson

Richard Schiff, M.D.

Dorothy Scott, M.D.

Mark Soucie, Ph.D.

E. Richard Stiehm

Robert P. Wise, MD, MPH

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Opening Remarks

DR. SCOTT: Good morning. I think we will get started. First I would like to get through some housekeeping issues but I want to thank everybody for your attendance. I think it will be a very exciting workshop.

These are the announcements that must be made: Most importantly, no food or beverage is allowed in the auditorium. I think there is an enforcement arm here so you need to be careful. They want us to remove all food and beverages. Set your pagers and cell phones to vibrate. To activate your microphone, press the mike button. There is a message desk. That phone number is 301-496-4062. People can call in and leave you a message there. We are going to be asking our speakers for permission to post their slides on the FDA web site, and we will also be posting a transcript of this meeting.

Now I will get to the more interesting part of this. I want to thank everybody for coming

and I want to point out that we have some leading authorities, in fact many of them as speakers and panel members in the PID and IGIV field. We would also like to welcome the many manufacturers and sponsors that have come to provide their input. We have here today people from FDA, including our Office Director, Jay Epstein. We have CDC, CMS and many other people that, we are very grateful, have been able to come.

I would also like to thank the Immune Deficiency Foundation for co-sponsoring this event and for providing us with the connections that we needed to help get this agenda and these wonderful speakers. Ms. Marcia Boyle, who is the Chairperson and CEO of the Immune Deficiency Foundation, is here and she may say a few words after lunch.

Now, the outcomes and goals of this workshop are to identify the most important current issues in IGIV treatment for people with primary immune deficiency. What we would like to do, among other things, is identify a possible research focus that would be important both in the laboratory and

clinically; and to ponder potential solutions to current issues and problems that we have identified. I would ask everybody, please, to participate in the discussions that we have. I think it would be very useful and it will help us to generate some outcomes.

Now I would like to introduce our keynote speaker, Dr. Hans Ochs, who is a Professor of Pediatrics at the University of Washington, in Seattle. He has devoted his career to the study of primary immune deficiency and to the clinical care of the people with primary immune deficiency. He has been present at workshops and speaking since time immemorial. I couldn't go back far enough through the workshops to find one where he hadn't participated. We are very pleased to welcome him, and thank you for setting the scene for the entire workshop.

Perspective on History of IGIV, Current Important Problems and Questions in the Field

DR. OCHS: Thank you, Dr. Scott. That

makes me feel a little overdue for the next phase of IGIV research; this morning in the taxi I heard that IGIV was successfully used to treat Alzheimer's, so I am in line for preventive therapy.

I have the task to provide you with some retrospective ideas about IGIV, some of the things we are doing now and some ideas that we will have to work on today to create a better future for IGIV. This slide is just intended to point out that the idea about passive immunization is spanning two centuries, going back to the 1890s when Behring and Kitasato found that serum has something that prevents the effect of diphtheria and tetanus toxin.

As we go down the line, we learned that the antibody activity is in the gamma globulin fraction. For that, we had to have a way to separate proteins in the serum. We learned how to fractionate plasma, creating Cohn Fraction II, which is the basis of IGIV. Bruton discovered that there was a disease where gamma globulin was

required for treatment, namely, X-linked agammaglobulinemia. Then, one of my favorites, Silvio Barandun, in the '60s, started to give gamma globulin intravenously with very interesting results--clinical studies that would not be possible today. Then, in the '80s we learned how to manipulate Cohn Fraction II properly to make this gamma globulin useful for IGIV injection. This is one of the hallmarks of the creating of IgG product, finding that the antibody activity is in the gamma globulin fraction. Very simply, plasma was separated based on the charge of the molecules and the size of the molecules.

Around the same time, the secret of IgG was revealed, knowing now that these molecules have a heavy chain and a light chain; that there are variable regions; that there are constant regions which are the different genetic control and are the different isotypes. We also learned on the way how nature is putting together this incredible variability of these antibodies by putting together Vt pieces and then, on top, that there is a

possibility to change these things somatically due to somatic type of mutation which is not genetically determined. So, we have a final output that can adapt to almost any foreign protein or polysaccharide.

That is Silvio Barandun at the time when he used Cohn Fraction II for intravenous use, and it is striking to read these papers of his. He would take Cohn Fraction II and inject it in normal controls, and he found out that 1/10 would have an anaphylactic reaction. If he took patients which looked retrospectively like common variable immune deficiencies, he would give this Cohn Fraction II in very small doses and 9/10 would have an anaphylactic reaction. He also learned--and this was very important for me later on--he found out that patients who underwent this anaphylactic shock were refractory for 3, 4, 5 days. So, when we did the first intravenous studies we actually primed the patients with a small dose of these not very well designed intravenous preparations, and then the next day they could tolerate the material very

well. This also indicates to me that more frequent infusions of IGIV are safer--let's say once every 2 weeks instead of once every 4 weeks.

So, at the beginning of our journey of IGIV some principles were put down which are now common ideas: highly purified immunoglobulins with no preservative; of course, no infectious agents and we learned the hard way that we actually infected some of these patients with hepatitis C. It should be monomeric or dimeric, not having many aggregates, and biologically active. IgG subclasses should be distributed relatively normally and then, of course, we need to have a broad spectrum of antibody activity, which we have essentially created by using many units for one batch of gamma globulin.

This is the result of one of the first IGIV trials in the United States. It was a product from Hyland and we called it modified immunoglobulin in glycine. They called it modified IgG. Then, after seeing this huge amount of side effects, with 76 percent of all patients having

relatively serious side effects of pain and fever and chills, and more than half of the infusions were associated with side effects, a simple step was taken, adding maltose to keep the aggregation from occurring and that reduced the side effects dramatically.

I have another slide showing this, during the same study. If you take the number of infusions with side effects--this is the modified immunoglobulin in glycine and the red one is in maltose, 10 percent maltose--and all these reactions markedly disappeared if the sugar was added to this preparation.

This was in the lab. We take Cohn Fraction II at 20 degrees and just keep it for an hour or half an hour at room temperature. Then, if you take this Cohn Fraction II, which was the intramuscular gamma globulin, and heat it for half an hour at 61 degrees Centigrade, which is not usually aggregating protein but in this situation you got a significant aggregation of IgG. If one added to Cohn Fraction II maltose at 10 percent,

you could totally prevent the aggregation of protein, and the same thing happened if one used the mitigated IGIV with glycine and added 10 percent maltose. It also withstood this trauma at 61 degrees.

When we looked a little further, this is the optical density--you know, the "Milky Way"--and this one is the time at 61 degrees. This is all Cohn Fraction II. If one takes Cohn Fraction II as it is and incubates it, it takes a long time, almost half a day, to get significant aggregation. If one adds methanol, a small amount of polyethylene glycol, this increases markedly this aggregation at optical density of 660 nm. If one takes the same preparation, Cohn Fraction PEG or methyl alcohol, and adds 10 percent maltose this aggregation is almost completely inhibited.

Now, what is the therapeutic action? Today I think we are mainly talking about replacement therapy but IGIV also has anti-inflammatory action. It can induce Fc receptor blockade which we use for IGIV in

autoimmune diseases. There is an anti-idiotypic autoimmune phenomenon. There are anti-idiotypic antibodies in IGIV. Then, of course, it has an effect on complement components.

The primary use for my field of interest and of today's meeting is IGIV in primary immune deficiency diseases, mainly those which have a predominant antibody deficiency like X-linked agammaglobulinemia as the hyper IgM syndromes which consist now of at least five genes. One of them is a T cell-related gene. This is CD40 ligand which also has an effect on the production of immunoglobulin common variable and then IgG subclass deficiencies if it is associated with antibody deficiency. Then, SCID patients either before bone marrow transplantation or some after bone marrow transplantation, if a B cell defect is remaining will depend on IGIV.

This was one of the early attempts trying to figure out how to treat these patients. If one gives the old dose of 100 mg/kg, as is shown here, once a month that is not enough to raise the peak

nor the trough level. If one gives 200 mg/kg every month one gets a modest rise in the peak level and also a rise above the baseline of the trough line. If one gives 400 mg/kg once a month one gets a further rise in the peak and a further rise, and it levels off later, of the trough level. But you can see this huge difference between peak and trough level. If one gives 200 mg/kg every 2 weeks twice a month you get a much more stable level with less of a difference between peak and trough. If I would give it every week, like 100 mg/kg for a total of 400, you would get even a more steady line. What actually happens during the interval between the infusion and the trough level is a complex way of intrinsic IgG, which may not be worth much, or material from old infusions, the last infusions, and this infusion and so that will determine what actually the peak level and the trough level in a specific patient will be.

The serum IgG concentration depends on a number of factors. One, of course, is how much milligrams/kilogram per week, 2 weeks or 4 weeks

you give. The route of injection--intravenously you get these high peaks, low troughs; intramuscularly it is painful but it guaranties a more level IgG serum concentration; subcutaneous, which has recently been propagated, is a way to have a very stable serum IgG level. The frequency of infusions, once a month or once a day--the peak level is important because you determine the trough level. The catabolic rate may be different from patient to patient or within a patient. If a patient has an acute infection or is malnourished the catabolic rate will go up. Losses, specifically in the bowel due to chronic bowel disease; and then hydration and also the half-life of a given preparation which we now always determine by pharmacokinectic experiments.

I wanted to show you the impact of immunoglobulin on this family which is from Montana. This is a lady born in 1892. She is probably a carrier because one of her daughters is a known carrier on whom we actually did some molecular analyses. Then, two of her sons died in

early infancy of infections. This lady has had three sons. One was born in 1944. He died at the age of 4 and did not have the luxury of getting treated properly with penicillin. He died of pneumonia. The next two sons were born in '47 and '49, way after penicillin was available. Both survived but they were not treated with immunoglobulin intramuscularly until they were teens and so they have both had lung surgery. They both had severe bronchiectasis.

This patient, I will show you later, developed ECHO infection, ECHO encephalitis, and was the first one treated with high dose IGIV. This one is doing well now. The only complications he had at the age of 43 was cancer of the colon, which is not unusual in patients with X-linked agammaglobulinemia.

This gentleman had a sister. She had a young son in 1968. He was born at the time when I saw his two uncles. He was diagnosed very early and is doing well. This is a carrier female, of course, of this gentleman. She has a son. He was

diagnosed at birth and both of those are doing very well on IGIV. Actually, this one was placed on intramuscular and subsequently on subcutaneous. He is now in his 30s. That is this individual.

I wanted to show a little bit more about this patient, who developed, at the age of 25, an ECHO infection with slowly progressive CNS symptoms. He had all these clinical findings with loss of cognitive skills. He got paresthesia. He had seizures. He had a peculiar dermatomyositis-like phenomenon of indurated skin and muscles, and this was due to a myositis/fasciitis and these patients have an increase in CPK, alkaline phosphatase and transaminases due to loss of muscle mass.

The impact of IGIV was quite striking. In 1990 a survey was done of 34 centers and this identified 248 XLA patients. The incidence of ECHO infections before 1985, when IGIV was being introduced, was 39. It is a rough estimated. After 1985 there were only 4 infected. Three were atypical and only one had not been on IGIV by the

time he developed this disease. I think it was a patient which Dr. Stiehm knows about. After he developed this ECHO infection this diagnosis of XLA was suspected and he was subsequently treated.

There you see this infiltrate of lymphocytes, T cells into the fascia, and the viruses are distributed in the muscle and the fascia. This first patient was treated. He developed this disease just about a year after the first IGIV preparation was tested in the laboratory, and he was treated with more than one liter of IGIV and his symptoms completely disappeared.

Safety--of course, we do not want to have any infectious agents in the material. The only one I am really aware has caused problems is hepatitis C. HIV we, fortunately, avoided. Parvovirus is probably neutralized because there is a lot of IgG antibody, and the question of prions is still not completely resolved. We do not want aggregates. The pH should be a little on the low side. Osmolality is really an issue in some

patients who have either chronic renal disease or who have cardiovascular problems. Low IgA--this is a question. I don't think many patients have actually a problem with this. Limit the rate of infusion, that means you should not, I think, overdo the amount of IgG per hour. Then, if there are problems we just reduce the interval between infusions and that usually takes care of these general problems.

The safety is pretty well now under control with antiviral steps, at least three per preparation. There is viral partitioning during the cold ethanol fractionation which has made this material safe from HIV. There are antibodies are in the IGIV that would, hopefully, neutralize remaining viruses. Low pH is helpful. Beta-propiolactone or caprylate treatment has been used. Solvent/detergent; pasteurization and, most recently, nanofiltration and UV light has been used to reduce that problem with antiviral steps.

Adverse events are still a problem. There are general reactions, especially during the first

and second infusion of new patients. There may be anaphylaxis, which is extremely rare but it can happen, especially now if you have the subcutaneous Cohn Fraction II if it would inadvertently be given intravenously. Acute renal failure is a problem probably due to high osmolality. Then, there is a problem with the cardiovascular system, volume overload and that can lead to thrombotic events. We have seen a few cases of Coombs positive hemolytic anemia. In fact, one or two preparations, when tested in clinical trials, had positive Coombs test for 1, 2 or 3 days without hemolysis. Then, of course, the CNS aseptic meningitis which is probably also due to overload in terms of osmolality.

I just want to point out to you that these general reactions are almost always during the first infusion of CVID patients or when patients are infused when infected. These are to some extent rate related and infusion interval related. As I mentioned, if the interval is too large these patients accumulate--this is a

hypothesis--accumulate immune complexes and will have problems.

I don't want to go into the details, but for the first infusion we do very careful monitoring. We monitor the rate of infusion of the material. The dose is usually 400 mg/kg and we measure carefully vital signs. We pretreat all these patients when they get their first infusion with Tylenol. Then we have infusion rate that slowly goes up and if there are reactions we have two ways to treat this, one, with SoluCortef and the other is Benadryl. We insist that the first infusion is done in a center where we know how to take care of these infusions. The second infusion is pretty much the same and then they are on their own.

So, for the subsequent infusions we do we always use, or most of the time we use 400 mg/kg every 4 weeks or 300 mg/kg every 3 weeks, and our favorite dose is 200 mg/kg every 2 weeks, especially for those who do self-infusion at home. It is no problem and that is the way we are

recommending to treat.

How do you dose? You have to know the baseline and you want to have a trough level that is at least 300-500 mg above the baseline. Then you may have to increase the dose or shorten the interval if any one of those events occurs, if the IgG level drops or if there is progressive pulmonary disease, or if the patient complains about having the "pre-infusion blues" and they lose interest, they are tired and sometimes they have infections. If they gain weight we have to adjust the dose, or if there are any problems with other adverse events.

Now, which preparation should we use? Is there any difference between preparations? There are low dose and low concentrations like 3 percent, 6 percent. There are high concentrations. People are talking about 16 percent intravenously but certainly subcutaneously or intramuscularly that is a good preparation. Should it be lyophilized or liquid? What is the osmotic load due to the formulation? We should look at viral inactivation

steps and antibody titers. Source versus recovered plasma is an issue and how many units of plasma are used for a single batch of IGIV.

Again, as I mentioned before, the dose you use every 4 weeks or 75 percent every 3 weeks, etc. Should one infuse in a center or at home by a nurse or at home by the patient or a representative of the patient's family. Then, we have to factor in the cost of this treatment. Is there any difference? And, what is the difference in quality of life. There are now interesting studies that address these issues.

Self-infusion at home is good for selected patients. It seems to me that is more common in the west than in the east of the United States. The positive aspects of that are that the patient becomes a partner. He can do potentially flexible dosing if it is a university professor; frequent infusions, every 2 weeks, there are essentially no adverse events. The overall events are 0.7 to 0.8 percent, studied by Brennan et al. There is clearly a quality of life improvement. The

negative is that there may be lack of supervision that has to be worked out. There may be missing of compliance and one may also miss complications, and in some areas there are potentially problems with legal complications.

That was our first attempt to teach these patients. These are all patients in 1981 in the clinical research center of the University of Washington. This gentleman was self-infusing himself. He taught these patients very effectively. The youngest patient who managed to do self-infusion was 6 years of age and he wanted to be as good as his 10 year-old brother, and this family is still self-infusing.

There are some rules. Never do it all by yourself, etc. It all makes sense. They have to be very carefully screened every 6-12 months at a center where they are known and where these tests can be carried out so that we do not lose them somewhere in the boonies.

The next self-infusion that is on the line, and that will be done in a second, is

subcutaneous infusion. In Sweden, for instance, over 90 percent of the patients do self-infusion at home of subcutaneous immunoglobulin. In Britain about half of the population; in the United States the clinical trials have been completed. I have about 10 patients on subcutaneous infusion. That is, of course, very easy. You don't have to find a vein. There are essentially no adverse events, 106 per 27,000 infusions in Sweden. In Sweden it is less costly. The problem, of course, again is supervision and the local reactions that seem to disappear over time with use of subcutaneous infusion.

That is one of the early clinical trials. This is on a dose of 200 mg/kg every 4 weeks IV. Then you increase to 400 mg every 4 weeks. That brings you up to a good peak and trough level. In this particular study one last dose was given of intravenous immunoglobulin to measure the half-life and the area under the curve. Then a last dose of IGIV was given followed by weekly injections of 100 mg/kg, practically the same dose as here. Then,

after a washout phase the area under the curve was determined. In order to equalize these one has to actually give more, about 130 percent of this. In Sweden they use this dose and they come up with very good clinical results. So, probably one does not have to change the dose.

So, to do this effectively one has to have in place instruction on how to do self-infusion. One uses 16 percent Cohn Fraction II as a dose per week. The abdomen or the thigh or the upper arm can be the site of infusion with a small butterfly needle. One can give locally EMLA cream. One can do it with a pump. The best is a syringe driving pump. The infusions take approximately one hour. There is a range. One can use more than one site. There is no premedication and it is okay for infants. As a matter of fact, you can do this by direct push without a pump once or twice a week. I have adult patients who inject themselves every day with the appropriate dose, without any problems, over 2-3 minutes.

How do we monitor? In practicality we

always ask the patients to write down the lot number. They have to be seen every 6-12 months for follow-up that includes now even a CT scan yearly. That is true for all of our patients.

I don't want to go into details but there are a number of different preparations, either lyophilized or liquid, that have different concentrations of IgG; that have different osmolality. Some of them have sugar or no sugar in it, and they have variable pH. There are two others recently on the market, Flebogamma and Carimune, again liquid or lyophilized, and in the future we will have to carefully look at these different parameters to generate the best formulation for this material.

That is Bob Good, who is also one of my heroes, if you wish, and I asked myself what would Bob Good tell us what to look for, and I think he probably would say we have to be absolutely sure that our preparations do not have prions.

He probably would also advise us that it is very important for the availability that

industry, that FDA, and that patients and doctors form a union and address these issues as best as possible. He would probably say it is not so important if it is liquid or lyophilized as long as it is safe.

He would also tell us that osmolality is important, especially for patients who can be hurt by hyper-osmolality like patients with chronic renal disease. He would ask the question how much IgG should we give in terms of concentration intravenously; subcutaneously, it is very clear as high a concentration as possible.

What about the sugar? On one hand, it is a very good way to stabilize IgG. On the other hand, it provides hypo-osmolal material. He would ask what is the role of spiking the material? Should we use hyperimmune serum, for instance, against TMV to add this to our immune preparation? On the other hand, should we use hyperimmune serum and take it out of the common preparations? Should we use monoclonal antibodies to spike in the future the common IGIV preparations?

What is the choice of infusion? I think he would probably say we have to just let the patients and the doctors decide do we give it IV,

subcutaneously or intramuscularly, and we have a choice now. So, for the patients it is getting easier. He also probably would tell us that we should simplify the procedure. Self-infusion is great if the patient can do it at home if that is a possibility. Should we do it every 4 weeks, which is the most unnatural way to do it? Should we give it once a week? Or, should we give it every day, the way we do it essentially? And, how can we save the enormous amount of dollars that are going into this form of treatment?

I will stop with this and apologize for going over time. Thank you very much. Any questions? Yes?

PARTICIPANT: Dr. Ochs, you mentioned a few things that I would like to ask you maybe to comment a little bit more about. One was the situation where some of the PID patients were getting ECHO encephalitis, and you showed there was

a drop after treatment but there are still cases--and I know from the time when I was looking after patients at the clinical center that even with treatment you still get PID patients with ECHO encephalitis. My question is should we be looking more carefully at the titers of the antibody, and do we know what titers are protective? And, once the encephalitis has established, is it difficult to really treat it? Is it more prophylaxis than treatment that is going to be effective?

DR. OCHS: There have been cases that occurred during IGIV therapy and I have observed two of them with absolutely good records. It is probably very important about what type of echovirus it is and what the titer of antibody in that particular preparation is. The problem is that there are many echoviruses. It could also be another virus. Polio, for instance, was a problem; Coxsackie virus; there is a JC virus. It is almost impossible to get the companies to check for all these viruses. So, we are in a blind alley there.

Originally the virology laboratories were

willing if we had the virus to actually titrate out different gamma globulin preparations. With the first person we did about 6 or 7 lots and there was a huge difference in specific neutralizing antibody, and we used the highest. That is no longer available. Even the CDC does not provide such service.

So, when I noticed these two cases I just told them to use alternatively two preparations, hoping that one of them would have a high titer, whatever came along. But I have sort of forgotten this, but this is one way to do it if you are worried. You know, it is like in the stock market. You don't want to put your eggs in one stock so you put it in different preparations and just routinely switch. But that is very difficult to do and nobody is actually practicing this. But you are right, it still can happen.

There is another disturbing thing. One of Dr. Stiehm's former fellows put together a group of patients worldwide of 14 individuals who developed progressive CNS disease without any etiology, and

to the best of our knowledge did not have this enteroviral problem. Most of them died. I think there is one still surviving. We do not know what the etiology is. In some patients it could be this virus that has been associated in some patients, this JC virus. These patients have not been carefully studied. Those who were studied did not have prion disease. So, in addition to the known viruses, there are other events that can happen and we do not know if they could be prevented if we would have the right mixture of immunoglobulins in the gamma globulin preparations.

But the rate is much lower and the two individuals I have seen with the development of encephalitis during IGIV therapy, one survived and the other one died. It was interesting that both of these patients years before had ECHO encephalitis and they were consistently treated and they responded to the first course, and years later they presented with the same virus. So, it is probably in their system. I would assume that the lot they received prior to their second infection

was low in specific antibody.

PARTICIPANT: Can I follow up with one real quick question? You stressed in your talk the fact that if you give the IGIV more frequently, for example every 2 weeks, you are going to end up with higher trough levels. I wonder if you have any data? We have tried to find data which would show that and there are trends in some studies that we have looked at that show that towards the end of the 4-week period there is a slightly higher incidence of upper respiratory tract infection. But do you know whether it has ever been documented that more frequent administration would give you not only higher trough levels but reduce infection rates?

DR. OCHS: So, the question was if one gives more frequent infusions, let's say every 2 weeks over every 4 weeks, does one reduce the side effects from the infusions that are often seen following infusion every 4 weeks? Yes, formally I don't think it has been studied but the patients, and I have probably about 20 who do self-infusion

at home every 2 weeks, they report no side effects. You know, sort of anecdotally, if these patients are put in trials every 2 or 4 weeks, they tell me that they don't feel as well at 4 and then after the infusion they lay around for a day and have some headaches. But there are no formal clinical trials that specifically address the rate of adverse events if you give IGIV every 4 weeks or every 2 weeks. One more question and then we should stop this.

PARTICIPANT: Just a quick question, you showed in your early formulation studies that the presence of maltose minimized the adverse events. Then I notice that some of the new formulations don't have any sugars in them. Also, you showed in those early examples that if they heated there was a tendency to more rapidly form what looks like particles. Do you know if the adverse events were associated with aggregates? I mean, did they look by size exclusion chromatography to see if there were dimers, primers and so forth? Could you comment on kind of those concepts?

DR. OCHS: At that time we were less sophisticated and these tests were not done, but I noticed in this first preparation which was handed

to me in 1973 by Mr. Hardy, from Hyland, that if you looked at the light it was cloudy, there were so many aggregates. So, we used filters and that didn't improve it. Then I noticed that when you dissolved it, rather than in normal saline, in 5 percent glucose the patients tolerated it better. That was the extent of our sophistication at that time and I wish we would have done these other experiments.

Now, you can get the same effect by lowering the pH. I didn't show you this but if you go through the motion of adding polyethylene glycol or alcohol and heated you can prevent this if you keep the product at low pH. That was a trick used to have a low pH. They also had another trick, they put a little pepsin in it. So, they were regular alchemists at that time, the Swiss Red Cross Prof. Hessick and Barandun, and they mixed it together right away and when they presented it to

the clinicians it worked. But I think the newer formulations, for instance the new preparation that ZIB-Behring has, it has amino acids as a buffer. It took them a long time. I have known about this product for years while it was in development. But they have it pat and they did all these studies which you suggested, and there are no aggregates; they have either monomers or dimers. So, one can eliminate the need for sugar if one uses a good chemist.

DR. SCOTT: I just need to announce that the enforcement arm has asked me to ask people really not to eat because the staff here will get in trouble if the management catches you eating, and please take your trash out.

On another note, I think there are a lot of interesting issues to discuss and we will save some of those for the discussion section but I appreciate, Dr. Ochs, that you brought up the question of how to optimize dosing frequency and dosing amount because I think that is one of the still current issues.

For our session we have Drs. Buckley, Stiehm and Schiff to speak. I don't have time to introduce them thoroughly but if you look at your

handouts you will see that we have a brief biography. Just to say that these are all very eminent people in the field and we appreciate that they have been able to come and speak to us to bring up these issues. After the break we will have the panel session and I would also like to invite Dr. Ochs to come up for that.

I. IGIV Efficacy

Infections in PID Patients: Prevention of End-Organ Damage; Need for Practice Guidelines and Screening

DR. BUCKLEY: Thank you very much, Dr. Scott, and thank you for inviting me. I was asked to speak about infections in patients with primary immune deficiency diseases. I will just say at the beginning that IGIV isn't necessarily the treatment that works for all these types of infections because there are certain host abnormalities in certain patients that define their susceptibility to infection and you can't cure that with IGIV.

However, the organisms that are sort of characteristic of these other types of infections would be things that people who design IGIV products in the future might want to keep in mind, particularly if you follow Dr. Ochs' suggestion of spiking IGIV with monoclonal antibodies to certain infectious agents.

Just to give you an overview about primary immune deficiency diseases, this field, since Dr. Bruton discovered agammaglobulinemia in 1952, has just grown exponentially and we now are up to at least 120 different syndromes that have been described over the past 53 years. The main point is that these conditions are usually recognized only when the person gets sick because outwardly these people don't look any different than a normal infant, child or adult. Then, the other thing to remember is that if you don't recognize it, and usually they are not recognized, then the problem is that you end up with permanent organ damage. Dr. Ochs has already touched on one of these. This would be central nervous system damage if one

develops a persistent enteroviral infection.

This is a slide that I use when I speak to the residents at our institution to try to help them think about these conditions. In the past it has been helpful to think about the types of infections that you have if you have a B cell defect, or a T cell defect, or phagocytic cell defect, or a complement deficiency because there have been certain characteristic organisms that have been associated with these. That way, one can then select the test that would be more appropriate for this.

You notice also on this slide that I said the acquired deficiency diseases such as those that we, as physicians, cause when we give chemotherapy or immunosuppressive agents for infections that alter the immune system such as HIV. They are thought to be more common but for those in the bottom half of this slide we really don't know what the incidence or prevalence of these conditions is. They are thought to be more rare and it is for that reason that they are not screened for in usual

screening tests.

So, the way that these patients really are recognized is that they have increased susceptibility to infection. The caveat there is that this has changed recently because primary care physicians use antibodies liberally. We have had patients referred to us who have been to their primary care doctor every other week and received another antibiotic when they left, and they were not diagnosed until they were 5 or 6 years old because they were covered by the antibiotics. So, the classic presentation of immunodeficiency with meningitis, septicemia or osteomyelitis you probably don't see very much anymore because of the use of antibiotics. Since they do appear to be normal individuals on the outside, if they are taking an antibiotic and they don't have a serious infection the only way you would make this diagnosis would be if you had a high index of suspicion.

So, this has been the classic way of thinking about these diseases. If you have a B

cell defect, which would be the type of defect that IGIV would be most appropriate for, the organisms that people who have antibody deficiency syndromes are infected with most commonly are all the various strains of pneumococcus, staphylococci, H. influenzae, streptococcal organisms, mycoplasma organisms, and we have already talked about the enteroviruses and
Giardia. The site of these infections usually is respiratory, although it could certainly be septicemia or meningitis if one were not on antibiotics.

Whereas, for T cell defects you would think of things like CMV, EBV, the herpes family of viruses, and opportunistic organisms like PCP, and the characteristic of these infections would be that they would be severe and persistent. Whereas, people who have phagocytic cell defects would usually have problems with things that are on the skin or on mucosa, such as staphylococcal organisms on the skin or Pseudomonas. Now, Serratia marcescens used to be sort of the hallmark of a

patient with chronic granulomatous disease but that is changing, as I will talk about in a minute. They also have problems with fungal infections. Of course, the hallmark of a patient with chronic granulomatous disease is that they have boils, and if you have another type of leukocyte deficiency such as ALD, then cellulitis would be the presentation.

There are new syndromes that have been recognized, that I will talk about in a minute, that are characterized by mycobacterial infections and by salmonella infections. Then, of course, deficiencies of complement components. In the early components you would think of pneumococcal infections or staph. infections. Neisseria infections would characterize those that had defects in the late components. Of course, people with complement deficiencies often also have autoimmune diseases.

This has been sort of the standard way of thinking about these different diseases, but now that we are understanding more about the molecular

basis of these our thinking is changing, and I will talk about that in a minute.

Let me go back to the end-organ damage. This is a boy who has Bruton's disease and you can see that he has right middle lobe disease. So, if this condition is not recognized and infections with either pneumococci or H. influenzae or Pseudomonas develop in these patients, then they are going to get bronchiectasis. There have been recent surveys of people who are adults who have Bruton agammaglobulinemia, for example, who are living now into their 30s, 40s or 50s. I guess the encouraging thing that has happened since IGIV has been on the scene is that there are fewer patients now with chronic lung disease. Somewhere between 20 and 30 percent of the adults who are surviving who have agammaglobulinemia do have chronic lung disease, and many of these die from this condition.

The other thing to remember is that not only do they have lung disease but they have pan-sinusitis and, no matter how many sinus surgeries they have, they still are going to have

pan-sinusitis. The role of rotating antibiotics, of course, is crucial in the management of this because since IGIV contains only IgG there is no way of replacing your mucosal immunity, and even if it contained IgA, Dr. Stiehm, in his study, showed years ago that there would be no way to get the IgA out on the mucous membrane surface.

Hans has already talked about this so I am not going to dwell on this, but the reason that people who have agammaglobulinemia get these infections is that they don't have secretory IgA. So, when they have summer diarrhea and they develop echovirus infection, then the IgA is not there to prevent entry of this virus so then you have entry of the virus into the circulation, and then it crosses the blood-brain barrier. Another example of this, of course, is the live polio vaccine and many of the patients who have had these enteroviral infections have had this either from vaccine virus or from wild type polio virus. As Hans has already said, this condition still occurs. Fortunately, in a recent survey that was done by Jerry

Winkelstein's group the incidence of this has dropped dramatically since IGIV was developed. But, as in the case of Dr. Stiehm and Dr. Ochs, we have now 7 or 8 patients at our institution who have CNS disease and we have tried to identify the cause of this, and in most of these cases we have not been able to tell what the etiology of the central nervous system infection is.

The other end-organ damage, of course, is bronchiectasis. This is an adult patient with CVID who has bronchiectasis. Of course, this could be prevented by preventing the infection in the first place.

Many of the patients with CVID--those of you who are not working in the field of primary immune deficiency may not appreciate the fact that the molecular defect in most cases of CVID is unknown, but there is a phenotype where there is lymphoid interstitial pneumonia or there is splenomegaly or this is lymph adenopathy and this seems to be triggered by infections, and we don't know which infections are the main triggers but

they do have B lymphocytes and perhaps these B lymphocytes can proliferate even though they can't become plasma cells and make antibodies.

This is just a CT showing the enormous spleen and adenopathy here in the peritoneum in a patient with CVID. Often, as a consequence of the splenomegaly, they will have penias, such as thrombocytopenia and anemia and neutropenia.

Now that we are understanding what the molecular defect is in many of these conditions, we have to think about this in a different way rather than just thinking about B cell, T cell, phagocytic cell and complement. For example, in a recent review written by the group in France, whenever one has recurrent pneumococcal infections, obviously you would think of a B cell defect, but also those who have T cell defects because you need to have T cells to help the B cells. Of course, we know that defects of the early complement components can also lead to pneumococcal disease. Congenital asplenia is something to think about.

But there are two new conditions that are

characterized by pneumococcal disease. One of these is NEMO, nuclear factor kappa-B essential modulator, also known clinically as ectodermal dysplasia with immunodeficiency. IRAK4 deficiency is one of the new late innate immune defects that are characterized by pneumococcal disease. So, whenever a clinician sees a patient with recurrent pneumococcal infections, they have to think about a whole variety of different defects now that might be the basis for this.

Another concept is if one has a patient with mycobacteria and salmonella infections, then you have to think about either of interferon gamma receptor defects, IL-12 deficiency or IL-12 receptor deficiency or STAT-1 deficiency. All of these have been characterized by selective susceptibility to these mycobacterial organisms or to salmonella.

If you have a patient that has chronic Cryptosporidium infections or Pneumocystis carinii--these are not things that you would normally think of with an antibody deficiency but

patients with X-linked hyper IgM which, as Hans has already pointed out, is really a T cell defect--have infections with these two types of organisms.

Previously we used to think that Serratia marcescens was the thing that was going to alert you to the patient with CGD but now we are seeing all sorts of unusual infections in CGD patients, such as Trichosporon pullulans and penicillium infections; a lot of candida infections. This was reported recently by Dr. Bill Shearer's group in Texas. So, there are lots of organisms that seem to be colonizing these patients that we haven't known about in the past.

Then the new threats, and I think Dr. Scott is going to be speaking about this in her talk, are the West Nile virus; smallpox or exposure to family members immunized with smallpox; anthrax. Then varicella is going to continue to be a problem. Because VZIG is no longer available there will have to be some new way of thinking about how to prevent this type of infection.

So, what I want to talk about is how you get to the diagnosis without having infection. Just getting back to what I said in the beginning,

the incidence and prevalence of primary immune deficiency diseases are really unknown. There are various estimates but basically we don't know. I suspect that there are a lot of people who die of pneumonia or meningitis or respiratory infections where the death certificate says the cause of death is pneumonia, but it is possible that these people probably had primary immune deficiency.

There is no newborn screening, and even with the revised screening list that is possibly going to be coming out soon primary immune deficiency is still not on the list. If you live in South America or in the Middle East where you get BCG on day one of life, this is almost certain death for those who have defects in T cell function. As I have already said, because we live in an antibiotic era we don't have a classic presentation. A survey done by the Immune Deficiency Foundation, just a year or two ago,

found that the average time from the time of the first infection to diagnosis was 9.7 years.

These were the types of infections they had. They had--I can't read the top one up here--sinusitis, pneumonia, ear infections and bronchitis. These were the leading types of infections. Of course, this is what you would see if you were a primary care physician. You would see these types of infections and they are treated easily with antibiotics or supportive therapy. But when they occur repeatedly one should think about these conditions.

So, the current status of this situation is that there is no screening for any genetic defect of the immune system at birth or at any time during life, anywhere in the world. This is a major problem, as I have said, where a lot of vaccines are administered on day one of life and if you have a defect in any kind of cell such as a T cell or monocyte, then generally these infants will die.

The paradox is that the screening methods

are available and could easily be implemented if screening for these defects were accepted as a standard of care. The obstacle is that they are considered to be so rare that screening for them would not be cost effective.

Population surveys that have been done suggest that primary immune deficiency affects an estimated 50,000 persons in the U.S. and that these are at least as common as hemophilia, cystic fibrosis, Huntington's disease and phenylketonuria. However, we won't really know the true incidence until there is population screening.

In the IDF survey it was determined that half of all the people who have primary immune deficiency were not diagnosed until they were adolescents or older. So, speaking of cost, the cost of late diagnosis is a heavy burden of disease on the patient and leads to early demise. The majority of patients report two or more hospitalizations before diagnosis. The cost of hospitalization of these patients far exceeds what it would cost to screen for the defect and to

implement therapeutic or preventive measures.

This is from the IDF survey. You can see in this pie diagram that more than half of these patients have been hospitalized more than two times in their life before the diagnosis was made.

So, the only thing that really exists in terms of incidence data comes from blood banks where they are screening the donors and recipients because people who have IgA deficiency are often the ones who have unexplained transfusion reactions because of anti-IgA antibodies. A blood bank in Knoxville, Tennessee, where they screened something like 6,000 blood donors, found that one out of every 333 people who donated blood--and these are people who had to fill out a card saying they had no chronic infections, no chronic disease--one out of every 333 of these repeatedly normal donors had no IgA.

IgA is the first cousin of common variable immunodeficiency. People who have IgA deficiency can eventually become common variables, but genetically it appears to be related very much to

common variable. So, if you do the math and divide 333 into 280 million, it is pretty close to one million people in the U.S. who have IgA deficiency or some other form of primary immune deficiency. This would be just a guess.

IgA deficiency could be screened for by measuring serum IgA on a heel stick done when the hemoglobin is first checked in infants 10-12 months of age. You could do the same thing when the child is getting ready to go to kindergarten or to first grade when the pre-school immunizations are given. You could also check again when they go to college. These would be times when you would have captive groups of patients that you could screen for this defect. If the IgA level is found to be low then, of course, you would measure the other immunoglobulins, and if they are found early enough IGIV can be started before organ damage occurs. The final comment about this is that there are existing genomic and proteomic methods that would make screening for all of these defects for which the molecular basis is known possible at birth.

Turning now to another disease, and this is severe combined immune deficiency, these are 32 infants at our institution out of 144 that we have

transplanted, who died after bone marrow transplantation. You can see that CMV, adenovirus, EBV, enterovirus--most all of these deaths were caused by viral agents that they were infected with when they presented. None of them died of graft versus host disease. So, again, if one could recognize these defects early enough, before infections occur, then obviously organ damage or death could be prevented.

So, what is the prevalence and incidence of SCID? Well, it must be very low because it is uniformly fatal in infancy unless it is corrected by immune reconstitution. What is the incidence? Again, this is unknown. The literature says anywhere between 1/100,000 to 1/500,000 but I suspect it is much higher, probably at least as common as something that is screened for routinely which is phenylketonuria.

Just to give you an example of an existing

screening test that is available for this, if one did a white count and a manual differential on the cord blood you could determine the absolute lymphocyte count. Since SCID is characterized by an absence of T cells, that means you are missing 70 percent of your lymphocytes. So, all of these babies are going to be lymphopenic and that means that if you just recognize lymphopenia in the cord blood then the next step could be taken, which would be to do flow cytometry to see if T cells are absent.

This is just to give you an idea about lymphocyte counts. Normally they are much higher during infancy than they are during older childhood and adulthood. Unfortunately, the time that most of the babies were referred to us presented was around 6 months. The lower limit of normal is 4,000. Many of these patients had had blood counts done repeatedly and they weren't recognized because people didn't realize that lymphocyte counts are normally much higher during infancy.

This is just to show you the mean

lymphocyte count for all the different types of SCID at our institution. Here is the lower limit of normal and you can see that all of these are low. There is one exception here where there were maternal T cells present that gave a very high lymphocyte count but, even so, it was still below the lower limit of normal.

Just to show you how this could be applied, this is a pedigree that Dr. Jennifer Park had studied and found to be effective with X-linked SCID, and these are the carrier females. This mother was pregnant with twins and, for religious reasons, they did not want to do amniocentesis or chorionic villi sampling to find out whether or not the boy was affected because they were hoping that the little girl could be a donor for the little boy if the boy were affected. When she went into labor--they were delivered in our institution, you can see that a white count on the cord blood revealed that the little girl had a normal white count and a normal absolute lymphocyte count, but the little boy had a low white count and a low

absolute lymphocyte count. We immediately did flow cytometry, and you can see that the boy had essentially no T cells or natural killer cells. So, this diagnosis could be made at birth and we were able, on the basis of this, to transplant this baby.

You can see 6 months later that the little boy was as healthy as the little girl. It turned out she could not be the donor so we used the mother as the donor. So he is chimeric with his mother's T cells.

This is just to show you, because we have seen a lot of SCID infants at our institution and even though we have given genetic counseling, often they conceive other children. So, we have had cord blood shipped to us for studies right at birth. We had 25 SCID infants that we had delivered at our institution but then these were siblings. These were 14 healthy newborns.

You can see that there is a little bit of overlap in the absolute lymphocyte count. These are the normal controls and these are the SCIDs.

But if you set the cut point at around 2,500 and then do flow cytometry you would be able to determine. Another way that you could do this would be to base it on the fact that there is absolutely no overlap at all in the T cell count for the SCIDs versus the normal infants. So, a test that is based on T cells would be something that would be even more reliable than just the lymphocyte count.

So, as I have said, if you have found lymphopenia you would repeat this just to make sure it wasn't a lab error and then you would do flow cytometry. And, if there is an absence of T cells the diagnosis would be confirmed by T cell functional studies but the patient would be placed in isolation. You would have this information immediately at birth. Of course, if you made the diagnosis the condition could be treated without doing any pre-transplant chemotherapy, and many times this can be done as an outpatient and the cost of doing this as an outpatient is around $50,000 whereas, if the child gets sick and comes

in at 6 months of age it can cost up to a million dollars for intensive care unit treatment.

This is just a Kaplan-Meier to show you 39 SCIDs that we have been able to transplant in the first 3.5 months of life. You can see that we have only lost two, one from CMV and one from EBV.

I am going to skip this and talk about this. One of the objections that we have to the suggestion that routine lymphocyte counts be done on cord blood is that the neonatologists prefer to do all their newborn screening on the Guthrie spot. The Guthrie spot is a filter paper test that was developed by Dr. Guthrie 30 years ago when he was interested in diagnosing phenylketonuria. It is 5 drops of blood on a piece of filter paper that is shipped off to the state lab. On these drops of blood you can do many, many different tests. Most of these are done by mass spectroscopy. However, it would require a DNA-based test to do a study that would detect T cells.

This is just a cartoon showing you the basis of the test that is currently under

consideration. Whenever the germ line configuration of the antigen receptor genes is changed by rearrangement of these genes there are pieces of DNA that are cut out, and these pieces of DNA are excised form a circle and they are called signal joint TRECs. So, a new T cell that has just recently rearranged its antigen receptor would have lots of these pieces of DNA that have just recently been cut out.

Just to show you, we had blood stored on one of our SCID patients from pre-transplant and you can see that there are no TRECs present prior to bone marrow transplant. After bone marrow transplantation there are normal numbers of these pieces of DNA that had been excised. So, it is a very useful marker for T cells. Newborn infants characteristically have about 99 percent naive T cells so these naive T cells would be loaded with signal joint TRECs and, therefore, the Guthrie spot could be eluted and in a DNA-based assay one could analyze for this.

This is just to show you all the ones that

we had pre-transplant blood on, and you can see that there are only two that had any detectable TRECs at all. The lower limit of accuracy is around 100 here. Even placentally transferred maternal cells don't interfere with the TREC assay.

Jennifer Park and her group have recently developed an assay that can be done on the Guthrie spot. By taking just two punches out of one of these Guthrie spots you can extract the DNA and you can quantify these TRECs and then this would be a measure of T cells. She was able to get from the State of Maryland the filter paper spots that had been shipped in on two babies that she later determined had X-linked SCID. So, she was able to retrieve these Guthrie cards and show that they did not have any TRECs, whereas these are various controls here that were all positive for TRECs.

So, the TREC assay is a promising tool for large-scale newborn screening for SCID and future studies will determine whether or not this is going to be practical. Many sites don't have any DNA-based testing for newborns but I think this is

all going to change in the future.

So, if you don't have screening, then how else can you find these people before they develop infections? One of the things that the Immune Deficiency Foundation is trying to do is to develop clinical care guidelines. A clinical care guideline or practice guideline was defined by the Institute of Medicine as guidelines that are systematically developed statements to assist the practitioner and patient decisions about appropriate health care for specific clinical circumstances. These statements can also be used for quality improvement and payment policy making.

So, last spring the Immune Deficiency Foundation had a committee that was charged with developing these guidelines and these are, hopefully, going to be released in the not too distant future. They are written so that patients and their families can understand them and call their physician's attention to the most appropriate testing and treatment that is currently available.

Since there is no stronger advocate for

the patient than the patient himself or the family of the patient, hopefully, by having this in a site where patients and families can read this, even if the physicians caring for the patient are not a hundred percent up to date on primary immune deficiency or the treatments, at least the parents will be able to notify these physicians about this. So, hopefully, this will help early detection and prevent organ damage. Thank you very much. Yes?

PARTICIPANT: I think, if I understood correctly, you were saying that in Bruton's agamma you were still seeing the 30-40 percent increase in chronic lung disease at ages of around 30-40. Is that true? Did I cite you correctly?

DR. BUCKLEY: Well, the surveys that have been done, they have been done on adults who are now, you know, between 20 and 40. IGIV, as Hans said, was not put on the market until 1981 so these people who are adults now would not necessarily have benefitted from IGIV throughout their lifetime. But there are still some cases that are occurring and, as Hans said, even in those who are

getting IGIV so there are unknown infectious agents that appear to be affecting these patients.

PARTICIPANT: The point that I wanted to make is actually a challenge to current immunological dogmas that IgA is so important for protection against mucosal immunity. I mean, there are two reasons why I think that should be challenged. One is that patients with selective IgG deficiency rarely get into trouble with infections. The other is that studies with vaccines have shown that if you get high enough IgG titers they actually diffuse across mucosal areas, and in the AIDS field papers have been published showing protection with only IgG in the vaginal mucosa protecting against AIDS.

DR. BUCKLEY: Well, you are absolutely correct. The reason that people with selective IgA deficiency don't get this is that even if the enterovirus penetrates the gut mucosa and gets into the intravascular compartment they have circulating IgG that can deal with it. But the problem is that the gamma globulin preparations, as Hans said,

didn't necessarily contain high enough titers against all of the different serotypes of the echoviruses. So, it is possible that a person can mount a very strong IgG response to that specific ECHO type and can deal with it. We monitored actually patients with IgA deficiency for these enteroviral infections and found that a number of them did have them in their GI tract but we never found them in their bloodstream or in their CNS. So, I think you are right that IgG can deal with it and I think that accounts for why we are not seeing as much of it as we did previously.

PARTICIPANT: Can I ask you a question?

DR. BUCKLEY: Yes.

PARTICIPANT: When you were talking about screening [not at microphone; inaudible]... a subset of individuals with IgG deficiency who also have [inaudible]... would you give an estimate or guesstimate as to [inaudible]... IgA deficiency [inaudible]... IgG replacement therapy. How many IgA deficient individuals do you think you would have to screen that way in order to identify one

who had an IgG deficiency?

DR. BUCKLEY: Well, I really don't know because, you know, it all gets back to the fact that we don't know what the incidence or prevalence of these defects is since no one ever tests for them. But I know that for families that I have evaluated where there has been IgA deficiency there has been, like, a sibling who had common variable. I have seen IgA deficients convert into common variables. So, even if you just detected IgA deficiency it would be worthwhile doing because these people do have health problems. They have autoimmune diseases. They have increased risk for cancer. There is a whole lot of other reasons to screen for that, let alone the fact that they would be at risk for transfusion reactions if they were to be given a blood product that contained IgA. Thank you.

Surrogate Markers for IGIV Licensure

DR. STIEHM: It is a pleasure to be here. Whenever I give a talk early in the morning in a different time zone I am reminded about my

experience in Amarillo, Texas. I was asked to give a talk at eight o'clock in the morning and I get there, and there is an auditorium about this size but there is only one person in the audience. I thought, oh my God, I must have the wrong time but I looked and it was the right time; and I thought it might be the wrong date and I checked my calendar and it was the right date. So, I gave my talk and the man applauded, asked me a good question and then as I was leaving the podium he said, "where are you going?" And, I said "I am going back to Los Angeles." He said, "you can't go; I am the second speaker."

[Laughter]

What I am going to speak about this morning is a possible alternative to our current method of allowing new IGIVs on the market. Currently, if you want to develop a new IGIV and want to release it you have to round up around 40 antibody-deficient patients that have profound deficiency and give that individual IGIV for 3 or 4 weeks for about a year, 400-600 mg/kg/month, and

compare the frequency of infections with the prior IGIV. Very often pharmacokinetic studies are done at the fifth or seventh month on a subset of these patients. Immunoglobulin levels are measured at several points, and you record serious infections, and the FDA now requires one or less per year, other infections, fevers, antibiotics, hospital days, absences from school or work and possibly physician visits.

So, is there a need for surrogate markers for IGIV testing? Well, first of all, new products are entering the market. Secondly, patients with XLA and common variable immunodeficiency, the ideal patients to test this new product, are fairly rare and they may not want to participate in a new IGIV trial and have all these blood tests done, etc. And, the current trials may not pick up an illness, such as varicella which these patients are susceptible to, even though a crucial antibody is missing because in that year they simply are not exposed to that.

So, a proposed alternative for IGIV

licensure--well, first of all, the IGIV must have a good safety profile. It can't be infected with pathogens, and the side effects must be acceptable, as people have talked about and as we will talk about more.

Secondly, the IGIV should have a good half-life, around 25 days, and I suggest that maybe that is even not necessary because the trough level will parallel the IGIV metabolism. The IGIV must provide adequate trough levels of IgG and IgG subclasses. So, I propose that maybe surrogate markers could be acceptable.

Well, what are the surrogate markers that have been suggested for IGIV? First of all, IgG and IgG subclass levels; perhaps IgG or antibody for pharmacokinetics measuring the rate of disappearance of the gamma globulin or selective antibody. People have used sinus or chest x-rays or CT scans, possibly pulmonary function tests, possibly inflammatory markers as a way to assess frequency of infection, and my suggestion is maybe antibody titers would be the ideal way to do this.

First of all, what about IgG level as a surrogate marker? Certainly the IgG level, the trough level is a very strong indicator of the

amount of clinical benefit. It has been well documented that moderate dose IGIV of 400-600 mg/kg is superior to a lower dose, 100-200 mg/kg, in terms of decreased antibiotic usage; decreased days of fever and hospitalization; improved pulmonary function; weight gain; clearance of sinusitis. So, we have this important surrogate marker of simply the IgG level.

A recent paper suggested maybe even higher doses of IGIV may be better than what we now sort of regard as standard dose. This is a study out of The Netherlands, showing that for patients who received higher doses of 600-800 mg/kg, essentially double of what they were previously getting of 300-400 mg/kg, the number of infections decreased. The frequency and duration of illness decreased. Of course, the IgG trough levels increased dramatically. So, here you are comparing 660 mg/kg to 940 mg/kg and there was clinical benefit with

the possibility that, as people have brought out, maybe you are getting more gamma globulin into the secretions by giving these higher doses. Of course, they are much higher. This is the trough level; the lowest level.

Another concept is that there have not been demonstrated any clinical differences if the trough levels are comparable between different gamma globulins. In fact, Zuhrie et al. studied 3 different products in a comparison and could find no clinical differences of different IgGs. Schiff et al. also found in a study that there were no clinical differences in 4 different commercial products. More recently, Roifman et al., and we will probably hear more about this from Dr. Gelfand, studied a Bayer IGIV and found an incidence of acute sinusitis, 16/73 in an old product versus 7/73 in a new product, and the claim was that this showed that this was a better product than their previous product. However, there were no differences in 8 other infections and no antibody titers were done. So, I think this study

has to be taken with a grain of salt.

What do we know about IgG as a surrogate marker? Well, an optimal level is over 500 mg/dL. This level, as Dr. Ochs points out, is dependent on the dose, the frequency and the route, and I think that everyone agrees that milligram per milligram the subcutaneous will give you a higher trough level than does IGIV.

Now, IgG level is a very good correlate of IgG catabolism so maybe these pharmacokinetic studies are not necessary, and probably repeated subclass determinations are not necessary either. We know that the IgG subclasses do differ in metabolism and biologic activities, and more recent studies show that IGIV usually has a normal distribution of IgG1, IgG2, and IgG3, and IgG4 doesn't really make a lot of difference in my opinion, and with most of the studies showing that the IgG subclass trough levels are similar to IgG in the proportion that they are in the serum.

Dr. Ochs and his colleagues used pharmacokinetics as a surrogate marker, and he

showed, like most other studies, that if you measure the half-life of patients with antibody deficiency they actually have a more prolonged half-life and that the subclass half-lives were also prolonged. The study shows, like in other studies, that IgG has a shorter half-life than the other, but it is pretty good in antibody deficiency because they do have longer half-lives.

Morell et al. also used the disappearance of antibody to measure the pharmacokinetics of IgG, and again showed that in antibody-deficient patients the half-life of antibody is prolonged for 5 different antigens that are described here--hepatitis B, cytomegalovirus, tetanus toxoid, pneumococcus and H. flu.

So, what do I think of IgG pharmacokinetics? It is easily done. You can do it using antibody or IgG levels after 6 or more infusions to get rid of the old gamma globulin and that may be unnecessary because trough levels give you similar information.

Well, how about using pulmonary function

tests as a surrogate marker? By the way, your handout has omitted four of the slides that I am giving right now. Simple pulmonary function tests, like FEV-1 or FVC, are readily available--no good in children under six, of course. Pulmonary function tests are okay in adults if they have a lot of lung disease but for most of the patients I don't think that they are a very good surrogate. Chest or sinus x-rays might be a useful surrogate but, again, these often don't change dramatically, particularly in the short period of time you are testing for a new IgG.

What about the use of acute phase reactants? Cunningham-Rndles has some data using C-reactive protein, finding that it is a useful surrogate of frequency of infection. Several years ago I did a research survey of mostly infectious disease literature and came up with the 4 that I thought were the most useful surrogate markers for chronic infection, and these include a C-reactive protein, a procalcitonin, an IL-8 and mannose-binding lectin. There have been a number

of studies to suggest that a combination of these 4 might be better than any single one directly. Others, such as the sed. rate, C3, IL-3, lactoferrin and a number of other ones have been proposed but I think that some combination of surrogate markers might be useful if you are drawing, say, a blood sample.

Finally, what about antibody titers as a surrogate marker? I think these are probably the best. You have to consider which antibody should be measured; how should they be measured; what is the protective level; how often should they be measured; and are serologic assays equivalent to functional antibodies like hemagglutination titer versus a neutralization titer for a virus?

You have to consider what antibodies are in a donor pool; what are the most important illnesses that these patients are likely to get; what are the most important pathogens; and what are the less common antibodies that should be measured, protecting against smallpox.

Well, as Dr. Buckley has alluded to, we

know that patients with antibody deficiency are susceptible to a number of bacterial and viruses, as well as mycoplasma, ureaplasma, cryptosporidia, pneumocystis occasionally, and bacteria as listed above, particularly S. pneumoniae and H. influenzae. Enteroviruses, of course, are very important as we mentioned.

Well, if we look at what infections are occurring in these patients that are target patients, pneumonia, ear, nose and throat infections, gastrointestinal infections, etc. are common but other, less common infections, serious infections like meningitis, septicemia and osteomyelitis do occur and must be considered.

What is the cause of death of patients with XLA and common variable? Pulmonary infections are way much higher, particularly since we no longer seem to have as much trouble with viral infection--echovirus and polio virus were high in the past but are less frequent now; liver disease; hepatitis C; lymphoma; gastrointestinal disease; sepsis and miscellaneous.

When we consider what antibodies we should measure, first of all we ought to consider what do we immunize normal children for. We now have a

whole laundry list of vaccines that are given routinely--diphtheria-pertussis-tetanus, measles, mumps, rubella, Hemophilus influenzae type B, hepatitis B, polio, varicella zoster and pneumococcus.

Do we immunize high risk children? And these are, indeed, high risk patients. These include Pneumovax which picks up the other serotypes not present in Prevnar, meningococcus, RSV infection we don't immunize; we give them passive antibody; influenza, hepatitis A and then we have to consider what less common diseases do immunodeficiency patients get, such as Parvovirus, salmonella, Giardia, other respiratory viruses, hepatitis C, Cryptosporidia and then, of course, our sponsor here wants us to have a immunoglobulin that has adequate antibody titers to hepatitis B, diphtheria, measles, tetanus and polio. These are the statutes of the FDA.

So, what are the choices of antibodies? Well, my list includes what is common in primary immune deficiency and these are the pneumococcal titers and the H. infuenzae titers. What do these patients need prophylaxis against? Measles, tetanus, diphtheria, polio, hepatitis B, hepatitis

A and chicken pox. What is ubiquitous and unavoidable? Cytomegalovirus.

Well, do the antibodies vary from lot to lot? They certainly do for less common organisms. This is just one recent example of a study comparing antibodies lot to lot for E. coli, Staph. aureus, Staph. epidermidis and enterococci. The titers in Sandoglobulin versus Gamimune were strikingly different.

Even more important, Weisman in 1994 looked at both manufacturers and different lots from the same manufacturers and there were tremendous differences for E. coli, pneumococci, H. influenzae, Staph. epidermidis and group B streptococci. So, even product to product it is going to vary tremendously probably depending on

the plasma pools that they are derived from.

So, my conclusion is that there are significant differences in antibody titers to IGIV, probably less common for major pathogens like pneumococcus and Hemophilus, and these differences are particularly crucial if you are studying less common disease such as nosocomial infections in newborns, CNS enteroviral infections, RSV or EBV virus.

So, the antibody titers that I would test for if I was going to do surrogate testing for a new IGIV product would include H. influenzae; pneumococcus, 5 serotypes; diphtheria; tetanus; hepatitis B; measles, varicella zoster and cytomegalovirus. Polio is required in the product and wouldn't be used as a measure of efficacy because it is a very difficult antibody to measure and you get such low titers.

First of all, let's just discuss these in brief, what we are talking about. For pneumococcus, it is the most common organism causing respiratory infections in immunodeficient

subjects. We know what the protective titer is and we know that IGIV donors usually have protective titers to most of these, particularly when you pool them.

There was a product on the market several years ago called bacterial polysaccharide immune globulin. The plasma pool was derived from individuals who were given immunization to Hemophilus, pneumococcus and meningococcus and these had extremely high titers. But in 5 percent IGIV there is a fairly good titer. You can read the numbers in the handout. Following IGIV you get adequate trough levels. Dr. Scott has a paper that is going to be published that details these titers in more detail.

I think it is important to assess several serotypes by ELISA that are absorbed with cell well protein and all of these are present in Prevnar. One important consideration is should opsonophagocytic titers be done, and I would think that for the initial studies you should probably do both to make sure that these do correlate. Then

you might want to consider other serotypes that are not present in Prevnar but are present in Pneumovax.

Hemophilus influenzae is a second most common organism causing respiratory infections in PID. Again, 5 percent IGIV has adequate amounts of it. The post-immunization titers are greater than 300 ng which is well beyond the protective levels, and there is sufficient antibody in the trough levels following 400 mg/kg of IGIV that gives you protective titers.

For diphtheria it is required by the FDA--a rare epidemi--and, again protective titers are present although no one has ever measured the trough level of this particular antigen.

Every one needs protection against tetanus. Indeed, there was a study to show that you could use IGIV instead of tetanus immune globulin to provide adequate titers of tetanus antibody following injury that exposes you to tetanus. C. tetanus I think would be a very good antibody to have in this pool.

Measles, again, is one of these ubiquitous organisms. FDA requires that it be present in IGIV. There are a number of assays available. The

neutralization titer is sort of the hallmark of protection. And, we also know that IGIV inhibits responsiveness to measles vaccine following a large dose. For example a child with Kawasaki disease can't be immunized for 4 months following a large dose of IGIV. There have been limited studies of measles titers following an IGIV infusion and titers seem to be protective.

Chicken pox is ubiquitous and this is a serious disease in immunodeficient children. So, it is present in IGIV, particularly present in varicella zoster immune globulin which is used for immediate prophylaxis. There is a study to show that you can protect against varicella with 300 mg/kg, and rarely do patients on IGIV get varicella and, if they do, it is usually a very mild course.

Hepatitis B is also required by the FDA. These kids are exposed to multiple needles, procedures, personnel and they seem to be unusually

susceptible to hepatitis B and IGIV has adequate levels of hepatitis B and, of course, hepatitis B immune globulin has extremely high titers.

Finally, cytomegalovirus would be a good one to test for. It is an ubiquitous infection. It is present in blood products that these patients are exposed to and it often will cause severe infection in primary immune deficiency. We don't know what the protective levels are. We do know that IGIV contains cytomegalovirus antibody and cytomegalovirus immune globulin contains titers that are 2 or 4 times higher.

Some of the other organisms that might be considered for antibody titers would be Staph. aureus., Staph. epidermidis, E. coli, pseudomonas, HSV1 and 2, Coxsackie, echovirus, parvovirus and possibly others.

Other surrogate markers that have been used for IGIV for other indications--for ITP, of course, the platelet response and the duration; for Kawasaki disease, prevention of aneurysms, possibly inhibition of cytokine production and

neutralization of super-antigens; for newborns it is particularly useful to have antibodies to Staph. epidermidis or Group B strep. and possibly opsonophagocytic index might be more important. For transplant patients cytomegalovirus is a crucial antibody and possibly the inhibition of a mixed leukocyte culture.

So, my proposal for an IGIV protocol based on surrogate markers is to give IGIV for a limited number of patients; of course, do safety and infection monitoring; and measure IgG, IgG subclasses and antibody titers 4 times, at pre, 4, 8 and 12 months. You might want to do pharmacokinetics but I don't think that is really necessary; then have these sera available for antibody titers to other organisms.

The patient would be monitored pre and at several points during the trial, and you should also assess past and current IGIVs and measure these levels in normal adults, young children and older children, and possibly immunodeficient patients pre-treatment and after treatment as good

controls.

So, are all IGIVs significant? Well, there are significant differences in side effects. Antibody titers are usually similar for major pathogens; variable for less common pathogens and probably for functional assays. The half-life has minor differences. The achieved IgG trough levels have minor differences. Achieved IgG subclass levels have minor differences and the clinical efficacy has minimal differences.

In summary, I think we want a trough level of greater than 500 mg/dL. We want subclasses distribution similar to the IGIV administered; antibodies titers to the 12 antibodies that I mentioned. Pulmonary function tests and acute phase reactants may be done but I don't think are crucial. And, pharmacokinetics, functional antibody assays, x-rays and other antibody titers might be considered. Thank you.

DR. SCOTT: Can we ask speakers to identify themselves?

DR. PIERCE: Yes, this is Dr. Pierce from

the FDA. What can you tell us about the statistics that would help us to better understand where we are in validation of using and relying on the trough levels, realizing that you also recommended other things? For example, in the study that you mentioned that was a randomized study comparing a higher range of doses versus a lower range of doses I believe that the trough levels seen in the higher range dose group were much higher than 500 mg/dL.

Also, in running through the list of several authors who had looked for differences between different IGIV products in their studies, could you tell us something about the numbers there? What was the biggest difference that could have been missed between any two IGIV products given the sample size that they examined?

DR. STIEHM: Yes, I looked long and hard for head-to-head studies and they are really very minimal. I think I found three and they were a very limited number and certainly didn't divide into type of infection. But my overall karma is that there have not been significant differences

from one brand to another unless the trough level is different. I think that there is considerable evidence that trough levels are probably the best surrogate marker for infection.

DR. PIERCE: I guess my perspective would be that if it is still an open question as to whether there are differences in efficacy for prophylaxis of infections between different IGIV products that would be given in a dose that produced an identical trough level, then it would also follow that the reliance on the trough level--that the jury may still be out in that regard.

DR. STIEHM: Yes, I agree with that and that is why I think antibody titers in addition to trough levels would be important to measure.

IGIV for Primary Immune Deficiency: Antibodies Against Potentially Problematic Pathogens

DR. SCOTT: Just a general comment before I start, and that is I think we are in the position now of asking whether we need to and should deconstruct IGIVs with regard to antibody

specificities, and whether there is a way of knowing whether right now the products are optimally protective. I would point out that our impression at any rate is that IGIVs are studied in a subset of selected patients for the efficacy trials and, of course, that might not relate entirely to the population in the field that needs to receive IGIV for prophylaxis against infections.

But I think it would be useful to figure out if it is possible to learn if the IGIVs are optimally protective against the common pathogens and the less common pathogens, and one question I will have is how could we find that out? And, if we did find out that there was a need for improvement I think that would be very useful for the patients.

We are a little behind time so I will try to go through this in a moderate hurry. Thank you, Dr. Stiehm for your talk. It was very helpful and related to what I am going to talk about next.

Just as background, as was mentioned--all Ig products-- ctually we don't have anything in the

Code of Federal Regulations for IGIV products--should have a minimum potency against diphtheria, measles and polio. Now, why did this occur or why was this regulation made? It was made in 1973. There may have been some different epidemiological considerations and also testing considerations but this was intended to be a surrogate for product integrity and effectiveness, these tests. They are meant to assure a certain amount of lot-to-lot consistency of immune globulins and, by the way, they should all be, according to the Code of Federal Regulations, functional assays.

There are lots of reasons to measure other antibody specificities so that we can define the scope of product activity against the relevant pathogens that have just been discussed that commonly infect people with primary immune deficiency. They could also be used to address predictors of efficacy and they are important in viral safety in two fashions. One is that, of course, they have neutralization potential,

particularly against non-enveloped viruses but also envelope viruses that may inadvertently contaminate the starting plasma pool. In addition, at FDA and elsewhere it has been shown that during manufacturing antibody complexed viruses are partitioned away from the IGIV product. So, they are also important for that reason, for example, for hepatitis B. Understanding the other antibody specificities may help us at least estimate the likelihood of protection for primary immune deficiency patients against emerging pathogens. That is a subset of things that I would like to talk about.

IGIV is probably constantly in evolution with respect to its antibody specificity for the less common pathogens for which we are not vaccinated. So, donor epidemiology and manufacturing I think are the two main drivers of what antibody specificities you have. Donor epidemiology is based on disease exposures and vaccination status. I would point out that in the past decade at least, and longer, there has been a

change where natural immunity is less often induced because people have been vaccinated against certain pathogens, and the question is outstanding whether these natural, so-called, antibodies from people who have had natural infection have a higher avidity or are more long-lasting, or present in higher titers. Of course, the people with these immunities to the natural infection are now getting older and their antibody titers may wane. But it has been shown for measles, at any rate, that the antibody titers from a naturally acquired infection are higher than from a vaccine.

Manufacturing methods can affect the antibody's repertoire, particularly manufacturing methods that eliminate or damage IgG3 which is a more sensitive subclass to various chemical and enzymatic treatments. It can affect titers, for example, to measles antibody and others that have some IgG3 subclass represented.

I am just going to briefly go through all of these. We have pathogens with a changing epidemiology because of vaccination. An emerging

pathogen of interest is West Nile virus. We also have some that are introduced, at least these would be pathogens with certain immune deficiencies by the counterterrorism efforts and particularly people with primary immune deficiency, and the Immune Deficiency Foundation called our attention to this. We were worried when we had a mass smallpox vaccination potential and when the first responders were vaccinated that they would accidentally acquire vaccinia infection from vaccinated people and then become ill.

Nearly everybody here has antibodies to measles and there are very few cases per year. There haven't been any epidemics since 1997 and, therefore, there is no boosting of the population of people who have already had measles or been vaccinated. Of course, the proportion of donors to plasma pools born after 1957 is increasing so now we have more vaccinated people than we do people who had natural infection. Because vaccination results in lower levels of probably high affinity antibody to measles and certainly lower levels,

there has been a concern that measles antibodies will decline in immune globulins. We would like to understand whether this is the case.

Judy Beeler, in her lab at the Office of Vaccines, in collaboration with M-Y Yu and myself and some others and Suzanne Audet, have done some measurements on IGIV products for measles neutralizing antibodies, and these are from 166 lots from the years 1998-2003. These are actually subsetted into years but I didn't have time to show you that. Basically the point I want to make from this slide is that here you are looking at the geometric mean titers so the higher the numbers you have here, the higher the neutralization activity, and these are just various different products that were looked at and this is the source of the plasma pool.

What you will notice is that most of the products are quite similar but, interestingly, these two products are made using the identical manufacturing procedures and what you see here is that the source plasma lots tend to result in lower

titers than the recovered plasma lots. This is actually true now, we know, for two different products where the recovered plasma still yields higher titers of measles neutralizing antibodies. In addition, we have a product here with a somewhat lower titer and this we think is probably a result of the manufacturing methodology.

Varicella zoster is also a concern because people with immune deficiency are susceptible to severe disease. It is generally known that the supply of varicella zoster immune globulin may be severely limited due to non-manufacture in the future of this product at least by the current manufacturer.

There is a protective titer that has been defined by vaccine studies. Of course, that is in normal people. But the question was already brought up whether or not IGIV itself, any IGIV, can decrease the varicella attack rate or the severity in primary immune deficiency patients. There aren't any really systematic studies but there are some case series starting with immune

serum globulin looked at in the 1960s to 1970s, followed by more recent studies which show that IGIV may have provided partial protection as did VZIG to exposed pediatric oncology patients, so kids that were exposed to smallpox and were immune compromised.

There is one letter to the editor by Ferdman, in Pediatric Infectious Diseases in 2000, where he had three people with primary immune deficiency that developed varicella while on regular IGIV treatment. These subjects have received IGIV 7, 11 and 30 days prior to the onset of their varicella infection. So, this tells us at least--and we don't know what IGIV it is and I am not really sure it matters--but this tells us that it is not necessarily protective. Now, none of these children got severe disease. That was the good news. But we don't have a handle on those titers and we don't really know what would be protective. But if VZIG is in short supply I think it is important for us to have an idea where the patients will stand that are receiving regular

immune globulin.

In collaboration with CDC, we started a research project. We have requested from our manufacturers 5 lots of each product and the testing for anti-varicella antibodies is being done by Scott Schmidt who is at CDC. He will be comparing these IGIVs directly to VZIG.

The purpose of this is not to make a claim. Rather, it is to estimate the likelihood of protection for patients with the current IGIVs. We would also like to monitor trends in the products as the varicella vaccinated donors continue to predominate over the naturally infected donors over time.

We are also interested in looking at antibodies to West Nile virus and IGIV. Certainly people, especially with these mixed immune deficiencies, are likely to be susceptible to severe disease if they contract West Nile virus. Now, IgG titers in donors were reported by Mike Busch at the BPAC last October and he mentioned that in epidemic areas up to 5.3 percent of donors

might have IgG titers against West Nile virus. So, we would like to know whether or not there are yet any detectable anti-West Nile virus antibody levels in IGIV because anti-West Nile virus antibodies, at least in animal models, can protect against disease and, of course, we have concerns about the immune deficiency patients.

So, a project that we would like to start is to assess the emergence of these antibodies in IGIV, the lag time between epidemics and emergence of antibody and whether there are regional differences, and the relationships of titers to geographic collection practices.

Finally, I am just going to end with smallpox vaccination. The vaccination for first responders was announced. Half a million were supposed to be vaccinated. In fact, far fewer volunteered to be vaccinated but people with primary immune deficiency and the IDF are concerned about the potential for accidental infection, as I mentioned, and we wanted to find out whether IGIVs contain anti-vaccinia antibodies.

We had an IGIV bank of products collected in about 2000 to 2002, and we sent these off blinded to a number of different labs to look at

neutralizing antibody to vaccinia in the products. So, here you see the different products. These two are vaccinia immune globulins. This is the amount of antibody needed to neutralize 50 percent of the virus in culture. Basically, the lower you are here the better your titers because you need less to neutralize. What you can see is that all of the products had antibody to vaccinia and some of them might have had a little bit more than others.

We also studied some of these in vivo. We just selected lots with sort of medium range titers and found that, indeed, when co-injected with vaccinia into SCID mice they could increase the survival time, which I think is a useful parameter to look at, SCID mice being the very worst case for susceptibility to infection.

Finally, I want to end with a question. Is there a role for an IGIV repository for research purposes so that we can look at the antibody titers

to different pathogens over time? This would enable us to monitor trends in emerging pathogen antibodies, and it could enable us to at least estimate the potential amount of protection or lack of protection in these products against new pathogens. The purpose would not be to compare products though.

If such a repository were to exist, I would suggest that it would be comprised of 5 random lots of each product; that the aliquots would be coded and frozen; and that yearly deposits would be made into the bank by the different manufacturers. One important question I think, especially important to the providers of this material, would be who can request these for testing. I think certainly FDA would be among those and CDC as well, but also outside investigators and industry might be interested and that would have to be discussed with the people who are supplying the material.

Should the samples be blinded when they are sent out? I think yes. If so, when or should

they ever be unblinded? For FDA research, we would look at the antibody levels to common and emerging pathogens. We would code published information and, of course, any such program would be voluntary. There wouldn't be a requirement to submit these samples and that would be different from the lot release requirement.

I think that is all I have to say here. Thank you for your attention.

PARTICIPANT: The only question about the lot repository is that if you don't capture epidemiological data on the donors where you got the plasma from geographically you basically have a blind set of samples and it doesn't really give you the ability to tie it to particular kinds of plasma. I think you have to ask the manufacturers to put more information into anything they would deposit.

DR. SCOTT: Well, there are two ways of looking at that. One is that more information would be very useful in that respect, especially where we see differences within a product, the

lot-to-lot variation. On the other hand, people who are being treated with IGIV, of course, are receiving whatever lot happens to come to the pharmacy so in a way there is an advantage to looking at the spread. I wouldn't see any harm in collecting the information but we wouldn't want to target it to a certain epidemiology. An exception, of course, would be West Nile but that is a different matter and we are asking for samples separately anyway.

Now to Dr. Schiff. I know we are running over time but I think in about 10 or 15 minutes we will take our break. Thanks.

Are we Adequately Replacing Antibody in Patients with Primary Immunodeficiency?

DR. SCHIFF: Thank you, Dr. Scott. Thank you for giving me the opportunity to talk to this group. It is an interesting position to be following my three mentors, Dr. Buckley, Dr. Stiehm and Dr. Ochs.

My talk is going to overlap somewhat with Dr. Stiehm's because we didn't really talk about

these ahead of time, but I am going to take a little bit different approach to this, that is, not so much what can we do to study new products but to look at what we are doing now and are we achieving what we are trying to.

The reason that I have had a concern about this for a long time, and Dr. Scott also alluded to this somewhat, is that IGIV is made from normal healthy donors. Healthy donors basically don't have very high levels of antibody. The whole idea is that we have low levels of antibody and then we get infected and you start making more of the antibody that you need. We have seen this in several patients who, when they got infected, their specific antibody disappeared very rapidly. So, when you have an immune deficiency patient, they don't have that opportunity and so what we are giving them is really sort of a low level protective antibody that healthy people have.

Again as Dr. Scott alluded to, antibody titers may be falling. We have the situation of vaccine versus natural infection and I think she

covered that pretty well. I am concerned about things like H. flu because, again, we are looking at immunized donors, adults that are now having children that are immunized who are not getting the high levels of exposure that they did before and with a lot of these diseases like H. flu we are not seeing as much. But there are also other reasons why.

We have eliminated some of the high risk donors and I think we saw a fall in CMV titers after we eliminated some of the more high risk donors. We eliminated them because of the risk of HIV and hepatitis but, on the other hand, they also tended to have very high titers to a lot of other things that they were infected to.

One of the things I am going to point out and go into some more detail on the data that Dr. Stiehm talked about is that high levels of antibody may be needed for chronic infections, and we know very little about the antibody titers during clinical studies. We have really focused pretty much on IgG levels, and I think that is important,

but we really haven't focused very much on specific antibody. One of the things that we have found is that the recommended doses of IgG have increased over the years so what is that really trying to tell us? So, I will try to get into that a little bit.

Then, also for the IGIV preparations, are the in vitro titers relevant? We often use different assays than we use for evaluating patients. If we are evaluating a patient to see whether they are adequately protected we really should be using the same assay, but also is there a difference measuring isolated IgG versus the antibody in plasma where that is the way the tests have been standardized? For many things we don't know the protective levels of antibody. Dr. Stiehm showed you a few where we do, but there are also a lot where we don't and are those the ones that are really causing problems now that we have solved sort of the easier problems? So, basically, are the current doses adequate? And, you know, my question is was anybody else besides me concerned?

I think the fact that people in this room are here is testimony that we do have questions about this.

To become somewhat biblical, in the beginning there was intramuscular gamma globulin, and immunologists looked down and said it was good. So, we were very pleased with ourselves in the 1950s, the morning and the evening of the first day. And, indeed, it was. I mean a lot of infections, sepsis, meningitis and severe pneumonias clearly decreased, so much so that in 1957--the chronic infections were less protected but in 1957 when the British Medical Research Council wanted to do a study they determined that to do a placebo-controlled trial was unethical. So, we have never really had a placebo-controlled trial of gamma globulin and, of course, I don't think we ever will. But they did look at some doses and they suggested that 100 mg/kg/month was a little better than 25 or 50 but patients weren't very well characterized back in 1957. We didn't even really know about B and T cells at that point, and 100 mg/kg/month was pretty much the upper limit

that we could give to patients intramuscularly. Most people are just not tough enough to take more than that.

So, we started off with 100 mg/kg/month and the first IGIV studies used that same dose. You heard, you know, that we achieved about the same levels and we got about the same results. In fact, there were a few more upper respiratory infections in the intravenous compared with the intramuscular but we thought that was due to the fact that for intravenous they came back every month and for intramuscular they came back every 6 months and they weren't keeping very good diaries and they just didn't remember how many minor infections they had. So basically they were equivalent.

The first trial of high dose IGIV comparing 400 to 100 didn't show any significant difference, but the patients weren't carefully selected and, again, this was done quite a while ago. But Dr. Pirofsky did one study using 500 versus 150 and he found that if you really focused

on the chronic infections there was a difference in the higher dose.

There are some studies that Dr. Stiehm alluded to, and I will just show a little bit more data on that. This was a study published by Roifman and Gelfand in 1987, in Toronto, and the study design in this was 12 patients with hypogammaglobulinemia. All had chronic lung disease with pulmonary functions that were more than 25 percent below predicted. It was a 12-month crossover study, 200 versus 600, but there was no run-in or washout period. So, that meant that in the crossover there is a period of time when their IgG levels were changing but that was still part of the efficacy period. They evaluated the incidence of infection; measured levels and measured pulmonary functions.

The thing that I wanted to focus in on is that if you just looked at the dose of gamma globulin being given you couldn't see very much difference, but if you focused in on the IgG levels you saw that if the patient had IgG levels less

than 500 they had 23 upper respiratory infections versus 10 if it was over 500; 11 cases of pneumonia versus 3. So, the total was 47 infections versus 15 looking at the IgG levels alone.

They also looked at the pulmonary function tests and, again, you can see that the pulmonary functions at the high dose--in the closed circles and squares, either FVC or FEV-1--when they were on the high dose were better and they declined when they were crossed over to low. That is true for the FEV-1 as well. You can see the opposite was true when they were on the lower dose, they improved after going to the higher dose. So, again, that is good evidence that the higher dose was better than the lower dose.

This is another study that you saw some data on from Dr. Stiehm. This study was 9 months on the higher dose versus standard, and I will show you the doses in a minute; a 3-month washout phase and then crossed over. In this case we did have a washout period between the two. Again, the standard dose was 300 for adults and 400 for

children. We have always done things on a kilogram basis and maybe for children we really should be thinking about doing this on a meter squared basis to try to correct for that. But they liked to give the children a little bit higher dose. Then for the higher dose they doubled it to 600 mg/kg or 800 mg/kg and I think, for the most part, all these patients were treated once every 4 weeks.

But you can see again that on the standard dose the infection rate per patient was 3.5 or 2.5, with infection duration of 33 days versus 21 days. These are both significant. The days to first infection 82 versus 123. And you can see, as Dr. Pierce alluded to before, in this case at the higher dose they are getting levels of 9.4, very high. I remember when we first started treating patients we thought if we could get levels of 200 mg/kg at least for those who had some baseline IgG that we were doing well. Now we are starting to talk about levels of 9.4, which is getting up close to what the normal levels are in healthy adults.

I am just going to go very quickly through

their recommendations. They found that the high dose was better, but they still recommended that you start with the standard dose because some patients will do well. And, as Dr. Buckley alluded to, if you start patients when they are healthy and they don't have chronic disease they often will do better at lower doses and it is after they get chronic disease that it seems that we need the higher dose. Then, those patients that had persistent infections, more severe infections per year, then you increase. I am not sure that we should, you know, wait that long but the idea is that if the patients are doing well at low dose they don't have to go to higher doses. But many patients with chronic infections are going to need higher doses and maybe we really need to be achieving the levels of healthy adults.

Then in a study that I guess Dr. Gelfand may talk about later comparing Gamunex to Gamimune, they also looked at the data comparing low and high doses of IgG, those over 400 versus less, and you can see that both for Gamunex and to a lesser

extent for Gamimune there was a difference, but even more importantly, when you look at it in terms of trough IgG levels for both Gamimune and Gamunex you can see that there was a decrease, a progressive decrease in the incidence of validated infections. So, if you look at the total here--20 versus 18 versus 13 as you get to the higher doses. All of this is suggesting that the low doses seem to be fine for basically protecting us from blood-borne infections. I think if you have bacterium for example in the bloodstream it probably doesn't take very much antibody for that to be opsonized and phagocytozed but once you start getting chronic disease we need to start using much higher doses.

The question then is why is that? Dr. Stiehm showed some data for some of the things that we think are important such as pneumococcus and H. flu. but in some ways we don't know. There is a dispute over whether mycoplasma is important. Moraxella catarrhallis was a commensal organism when I was a resident and now seems to be a

significant pathogen. Are these other organisms responsible for causing some of these chronic infections, or is it simply a matter that it takes much higher levels of the other relevant antibodies, such as pneumococcus and H. flu., to just push it into these tissues where it is less available?

For the most part we have relied on the data for IGIV products for the information that we are providing. To show you one representative table, every product is tested against a wide variety of antigens but the assays are sometimes very difficult to relate to what we do and look at in patients. Again, I am still not convinced that taking an IgG preparation that now has either a glycine or a sugar stabilizer and diluting that out gives you exactly the same titers as the assays that have been standardized in plasma or serum for patients.

This is a very busy slide and I am sure you can't see it but you have a copy in your handout. But I just wanted to show that, you know,

at least we think we have good titers for things like H. flu. and pneumococcal serotypes. There is some variation from brand to brand and there is also variation from lot to lot but in general we think these titers are very good.

But for pneumococcus, I just wonder in some ways. If you go back to Jerry Schiffman's original data--and these are the pre-immunization titers for healthy adults and his assay is a little different so what he did is he looked at this, and he averages about 300 ng/mL in a normally healthy person. In fact, the so-called protective level is really based on the fact that healthy people have levels like that. It was never really based on what we can do in animals, and that is give a certain amount of antibody and then challenge them. So, we have never really done challenge studies in people and I doubt that the FDA would really approve of that. But I just wanted to make the point that most of what we know about protective titers is really done by inference as opposed to direct study.

Virtually every study that we have done has really focused on IgG levels, and it is a good surrogate marker. It does tell us that we are

replacing IgG but we have really not looked very much at specific antibody. There have been a few trials. We did a trial where we focused on looking at pneumococcal and tetanus half-lives, and we published the half-lives but we really didn't focus very much on how well we were protecting the levels. In fact, I want to go back and try to find that data and see if maybe we can really look at it in terms of what the absolute antibody titers were as opposed to what the half-lives were.

There are very few studies that have actually published titers. They may have done the half-life studies but they haven't published the titers. There are a couple of studies that have used opsonophagocytosis assays that do suggest protective levels in patients but, again, it is a little hard to relate that back and we have never done good studies where we have actually followed the titers. I think that Dr. Stiehm was suggesting

that perhaps we need to do that in future studies and really focus in more on protective antibodies.

This is one study that did look at antibody titers by either neutralization or CMV but these patients were on very high doses, 500 mg every 2 weeks. It is also 1992 and, you know, there is a suggestion that the titers at least titers may not be representative of what we can achieve.

So, in conclusion, I think the clinical data strongly suggests that higher doses of IGIV are more effective. I am not sure that we have even shown that we have max'd out on this. It does get to be a practical issue. Getting back to the question of how often you give it, if you do this more often there are a few things that happen. One is your peak and trough would rest to the mean. The other things is that we know when you give very high doses and when the level is high the catabolism is much higher; it is dependent on dose. So, if you give a very high dose your catabolic rate is higher and it is actually less efficient.

So, if we did that same dose that they did in The Netherlands and gave this every week, the same dose but divided every week, the trough levels probably would have been significantly higher and maybe we could get them at the same dose up to 1200 mg.

But for a lot of these we need to know what level of antibody is protective, and not only what is protective to keep us from getting an infection but what do you do once you are infected because, indeed, we are not only preventing infections in these patients but often having to treat them. At least for pneumococcus, I have seen the specific antibody disappear within 2 days when a patient became infected.

Again, what are the most relevant organisms? We focused in a lot on the ones that patients seem to get with acute infections but what about things like Moraxella catarrhallis or mycoplasma? Are these important?

Again getting back to what Dr. Stiehm said, are there other ways to determine this besides doing the big clinical studies? The

largest study ever done still had difficulty showing differences between the two products because it didn't meet statistical significance in any area and in the general infections it didn't. I don't think anybody is going to do any study larger than that. So, we do need other ways to do this to decide what antibodies we are going to look at. I think after the break we are going to have a panel discussion and see if we can address some of these issues. Thank you.

DR. SCOTT: Let's take a 15-minute break.

[Brief recess]

Panel Discussion

DR. SCHIFF: Welcome back, everybody. In the next 20 minutes we are going to have a panel discussion to go over some of the issues that were raised in this morning's talks. Twenty minutes isn't nearly long enough. I remember when I was taking a biochemical chemistry exam and my professor came by and just kind of glanced at my paper and he said, "well, it looks to me like you know what you're talking about today." I said, "I

don't understand; you couldn't possibly have read my answer." He said, "no, your answers are short and your handwriting is neat so I know you know what you're talking about." It was a good lesson to me. I think the less we understand the more we talk about it. But this morning we are going to talk about it for only 20 minutes.

Some of the things that I would like to try to address are the issue of the IgG level. I think we all agree that the IgG level is important but what trough level is important? Then, the other issue is, is the trough the only important thing? Is getting a high peak to really force the IgG antibodies into the tissues important? Is that of any relevance? Or, is just maintaining a high trough important?

We certainly should address the issue of antibody titers; which titers we are going to look at; which things are relevant for the patients. Dr. Stiehm outlined some of them. I brought up the issue of mycoplasma and Dr. Gelfand said he has looked in his IgG preparations and there is no

mycoplasma antibody. So, it doesn't sound like we can raise the dose high enough. Zero times anything is still zero.

So, there are issues. IgG doesn't cure everything and we need to sort of decide how we can focus and determine how we can do studies that are practical to answer some of these questions and, ultimately, I think also who is going to support them.

So, why don't we start off with this issue of the IgG level, what levels are improvement or peaks are important? Hans, do you want to start with that?

DR. OCHS: One problem that I see is what is a trough level really. What is important is what is above the baseline. So, the trough level alone from one patient to the next is probably not the absolute criteria because you may have a patient with X-linked agammaglobulinemia who has a baseline of 50 mg/dL and you may have a CVID patient who has a baseline of 450 mg/dL or 500 mg/dL. So, you would like to have one at least

500-600 mg/dL for the XLA patient. For the CVID patient you want to have above 1000.

So, my trend is to look at the baseline which is essentially the IgG level prior to treatment with IGIV. That is not so simple because we don't know if over the years that baseline changes either up or down. So, the ideal trough level is something that we have to make an effort to form an educated guess for, but that is one thing we have to consider.

The other is, you know, does the trough level reflect what the extracellular level is? For most patients that is important, in addition to what the surface level is on mucosal membranes. But, certainly, the peak level after the injection, the infusion of IGIV, represents only what is in the blood but not what is in the tissue, and the tissue level is also important. I think the tissue level is best estimated by the trough level. By that time there should be equilibrium.

That brings us, of course, to the question of should we maintain a high trough level like we

can achieve by giving either more or more often, every day or once a week? Subcutaneous gives you a much higher trough level than IGIV. So, these are all issues which we need to address and it depends on our clinical perspective.

DR. SCHIFF: Does anybody on the panel or anybody in the audience have data on antibody levels in tissue after infusions? Has that ever been addressed, especially antibody titers in tissue?

PARTICIPANT: I think it is very difficult to measure in tissues. By doing careful pharmacokinetic studies you can get some idea of tissue distribution but I think one relatively simple way to measure that antibody is getting to the right place is to take mucosal samples. That is my bias is, again, from the HIV work that I am involved with but isn't it very important here too? And, isn't it a lot easier to measure and assess looking at mucosal samples in vagina, rectum, saliva, bronchial secretions, rather than trying to find out what is in the tissues? We haven't tried

to get that data, and maybe that is something we should think about seriously.

DR. OCHS: Way back when I was a Fellow I tested the effect of bacteriophage on the antibody levels also in normal controls and, doing that, I had hoped that perhaps we would get mucosal antibodies. I personally, and some of my co-workers, sniffed the stuff. We never got any local antibody production. But if we looked at saliva or tears after intravenous injection we could estimate that about a tenth of a percent of the antibody titer in the plasma comes out in the tears or in nasal washing. So, there is a tremendous difference between what is in the serum, as you suggested, and what is coming out in the secretions, at least in the eyes and the nose.

From that point of view--you know, this is a crazy idea but maybe we have to give gamma globulin IgG locally either into the eyes as drops or as an inhaler. There is a very interesting paper from Dr. Martha Abel where she used a preparation of oral gamma globulin that was spiked

with IgA so we don't have only IgG but a combination, I think 60 percent IgA and 40 percent IgG. We looked at necrotizing enterocolitis and, again, it was not a good controlled, prospective study but in an intensive care unit in Vienna they had a certain amount--I think 40 preemies with necrotizing enterocolitis in a period prior to the use of this oral mixture and after that there was nothing, none. This was published in The New England Journal of Medicine and was forgotten. Nobody has repeated the same study with an IgG preparation. But locally one could address these issues if one would invest in clinical trials.

DR. SCHIFF: I know Dr. Stiehm has also looked at oral IgG and its survival in the GI tract. We know that it does survive. It wasn't a clinical trial but we know that IgG will survive passage through the GI tract.

DR. STIEHM: There has been a continued interest in local use of gamma globulin. There is a trial where they blew gamma globulin in the nose of kids, in Sweden, going to nursery school and

they did cut down the frequency of infection. There are 30 or 40 articles on the use of the inhaled gamma globulin in the treatment of pneumonia. So, people are still quite interested in local use of IGIV.

We have interesting anecdotal evidence. We gave a child subcutaneous gamma globulin and the warts fell off in the area where we gave him the subcutaneous. But I think that local use of IGIV is or interest.

One thing Becky just mentioned to me is that one of the problems is that if you have a local infection you are going to get more gamma globulin across into the mucosal area where there is inflammation. So, I think studies to try to address the fact that if you give a high dose of IGIV whether you get gamma globulin into the saliva or into the tears would be very interesting to suggest that maybe this peak is doing some good.

DR. SCHIFF: Dr. Scott, did you have a comment?

DR. SCOTT: I just wanted to ask the panel

and the audience do you perceive that there is a subset of patients that particularly may need different, or more, or other antibodies? Dr. Ochs mentioned the "pre-infusion blues" and I wondered if anybody knows of studies that show that any kind of infection seems to increase around the time of the trough level.

DR. BUCKLEY: I think there are no systematic studies that have been made to look at that. I might add that one of the things that we do in our division is to see patients who have been on intravenous immunoglobulin for many, many years who, we ultimately were able to show, did not have an underlying immune deficiency but they also had the "three-week blues."

DR. OCHS: What my patients often tell me is that their eyes get pink and the parents say the kid doesn't play as much. Then, after they get their infusion, 2 or 3 days later they want to put lead in their shoes so they run around less. Adult patients tell me also stories about the effect of IGIV. But there is really an invigorating part in

the beginning and a letdown prior to infusion. Of course, those are more or less anecdotes but I could write a book about it.

PARTICIPANT: Just a follow-up comment, many of our patients actually notice at the end of that 4-week period that they have some very subjective findings--you know, more tiredness; more runny nose; more sniffles--not documented infection but some of these other kind of non-specific complaints. You know, they have convinced me to go from every 4 weeks to every 3 weeks and it helps temporarily. Then we go to every 2 weeks and it helps temporarily. I think that is related to the fact that you are changing the catabolism. In other words, you are shortening the interval but you are probably changing the catabolism, although I didn't measure trough levels during these periods. Obviously it is not a satisfactory tactic to go from 4-week intervals to 3-week to 2-week intervals. Maybe subcutaneous will be different. I don't know and that remains to be seen in the studies.

DR. SCHIFF: I haven't seen that same phenomenon of having to progressively shorten. You had a question?

PARTICIPANT: I can't remember which study it was, but in one of the recently published licensure trials in the past couple of years the patients were allowed to be kept on the same dosage interval they had been on before and during the study, every 3 weeks or every 4 weeks. Then, when they come to the pharmacokinetic part after the fifth or seventh infusion of the study product, the pharmacokinetic phase is always carried out to 28 days, and in one of the trials it turned out that patients that had been on a 3-week schedule before entering the study--in other words, their clinician had arrived at that dosage regimen with them--those patients had a half-life of the study product of around 21 days. The patients who had been on a 4-week interval before entering the study had a half-life of about 28 days. In all cases the pharmacokinetic analysis was carried out for 28 days. So, I interpret that--it is a relatively

small number of patients, less than 10 in each group, but I interpret that to mean that the patient and the physician had sort of figured out that they had a different half-life before it was even measured.

[Multi-member discussion off microphone; inaudible]

PARTICIPANT: I just want to come back to a couple of comments. One is we also, remember, used to put IGIV or even intramuscular in devices when patients had chronic ECHO and encephalomyelitis. We even tried that, to no avail. But I always was surprised how few side effects there were putting it into the spinal fluid.

The other question is about the 4 weeks, the trough or the "blues." You commented on our study at 200 versus 600 and you saw very clearly in those that it wasn't the dose that was administered; it took time to achieve stable plateaus when we went from 200 to 600. It was only at that time that the infections began to be

eliminated. So, I think adequate dosing becomes an important issue.

The real issue I want to come back to is in a study that you quoted because the follow-up was the isolation of mycoplasma, particularly in the patients who had chronic pulmonary disease with bronchiectasis, and so on. The fact was that at the higher dose, if you looked at mycoplasma isolates over 6-12 months, you saw progressive decrease in the number of isolates with the high dose. But what was important to us--and it comes back to the whole peak-trough and that is why I asked you at the break--we should talk about gradients and getting stuff out of the blood into the secretions where they are going to be doing their protective action.

With mycoplasma, in particular ureaplasma but some of the others, normal donors never have systemic infections with these organisms. They are mucosal infections, causes of habitual abortion and so on in women. But the unique susceptibility in hypogams. is there. In fact, we can show

protection. You saw the improvement in pulmonary function. But when you look at antibody titers to the various serotypes in all preparations of gamma globulin it is barely detectable.

So, the question I think that we have avoided is mechanism of action to some degree of Ig replacement and, as part of this, some non-antibody-mediated protection, whether it is anti-inflammatory or whatever, because even in the changes in pulmonary function it was only a short period of time. It is hard to imagine that simple organism elimination caused these rapid changes in FEV-1 or FVCs. So, I think that part of this peak-trough issue that we have to contend with is the non-antibody-mediated effects as well. We know that in the autoimmune and inflammatory diseases the anti-inflammatory activities are best at the higher doses, not the repeated smaller doses.

DR. SCHIFF: In some ways the question is almost like the infectious disease people deal with for antibiotics, and some antibiotics, you know, are infused continuously because they work better

with a good baseline and others need a peak and trough. We have never really done our studies looking at that particular issue.

Let's move on a little bit, because we don't have a lot of time, getting back to what titers should we look at; how best to do this. I mean, I have alluded to the fact that I am not sure looking at the products is the best way. You know, when you are studying an antibiotic you put it into patients and see what levels you get. If we are going to evaluate our products, not necessarily comparing products but just in general, should we have some trials set up where we actually look at levels? Or, should that be built in as an adjunct to trials, not necessarily as part of the trial itself but as an adjunct while we are treating patients to try to get some of those data maybe without having to do additional studies just for that? So, Dick, I know this is one of the areas you are most interested in, do you want to comment?

DR. STIEHM: Actually, we did write a protocol for the Immune Deficiency Foundation but

it never got consummated. But I think a trial in which antibody titers to several different organisms is clearly indicated, and also to do the controls I mentioned, do it in patients that are adequately treated, patients pre-treatment and normal subjects, normal children. So, I am a strong advocate of having the FDA sponsor that.

DR. SCOTT: Well, in terms of measuring the antibody titers in the products themselves, I think we would regard that as a beginning really, and I think that somebody has pointed out that measuring them in the matrix that isn't serum or plasma might not give quite as precise information as otherwise. That can only be partially compensated for.

Even within that, there is the question of do you do functional assays, functional assays being much more difficult to come close to validation and have a low CV, but everybody feels--I think most of us feel that functional assays give you better information. We certainly have examples of binding assays where the

functional assays didn't play out to reflect the binding at all times because a lot of antibodies are non-neutralizing to organisms.

So, from the point of view of the idea of establishing an IGIV bank, I would like to get to that as well. I would like to hear people's thoughts about it, especially on distribution, how to collect it, how many lots. I would say that probably measuring levels in patients and knowing what the starting levels were in the product will be more informative and that would have to go along with clinical information as well.

DR. SCHIFF: Before we move on to the bank, Dr. Buckley, you had a comment?

DR. BUCKLEY: I would just like to remind you of what Richard said earlier, and that is that if somebody comes in with acute pneumococcal pneumonia the antibody titers to the pneumococcus are going to disappear very, very shortly. So, if you are going to do an antibody titer study it would be I think important to have as one of the variables whether or not they have bronchiectasis.

People who have bronchiectasis usually are colonized by H. flu. and/or pneumococcus chronically. That is why they are on rotating antibiotics. But you would imagine that they would be consuming the antibodies to both H. flu. and pneumococcus more than somebody who doesn't have bronchiectasis or pan-sinusitis. I think that would be one of the ways in which you could divide the population that you are going to study clinically. I expect that those people would definitely benefit from either larger doses or more frequent infusions.

DR. SCHIFF: I think there are a couple of different issues. One is trying to find out where we are. In other words, you can't necessarily build all these antibody titers into a trial, especially an indication trial, and use that as a means to decide if another product is good because we need to get the data first. You are sort of using the data and then going back and applying it. So, to begin with we really need trials, and they could be built in as part of an indication trial

but sort of as an aside, or they could be free-standing trials, which I think would have to be supported either by NIH or the FDA because I don't see industry doing that kind of basic science. But we need that information first, and then you could come to some sort of agreement as to which things are important; what levels are attainable. We can't decide--I can't remember the statistical term but basically you can't use your study to then decide what your results are going to be.

But why don't we come back to this issue of the pool? I think most of us would agree that it is a good idea to have these samples stored away but I think deciding on which ones, you know, choosing 5 arbitrary lots, do you choose some from different times of the year? How are we going to select those samples? The issue of who is going to use them, all these things are important but I think even more important is how do you select the samples so that you get a representation? We know things like West Nile vary strongly through the

year. Even the respiratory viruses, things like the enteroviral antibodies probably get much higher in the winter and then drop down again. So, how are we going to choose those? What data are we going to collect so that you could do correlates, and so on? Since we have all talked, what about the audience?

PARTICIPANT: There was a time a few years ago where we were talking regarding setting up studies to look for titers and trying to use that as a surrogate marker. The other aspect of it that I think should be emphasized is that having the titers maybe should be part of the release specifications for these products. As we are hearing the concerns from some of the speakers, with time some of these titers are going to come down, and are already coming down, and some of the products are going to be discontinued; the hyperimmune products are going to be discontinued. It would be a public health benefit to know what titers there are in the IGIVs that are available.

But something else that I think would add

to this discussion, and I think there is data out there when you look at vaccine trials--and I know Dr. Stiehm used that as part of his argument that if you look at vaccine trials for particular infectious agents and where antibodies are important or most important in protection, you can get data used to approve vaccines showing what titers are protective in humans for a particular infectious agent. So, some of that data is available and can be used I think to answer some of the questions that we are asking.

DR. SCHIFF: And we have some idea of infective levels for some of the vaccines, and even some of those are indirect evidence, not all of them, because it is often determined in animal studies what is protective and then you extrapolate that level back to people. But, again, I think you are right. I think for vaccines we have some idea but lots of other organisms we don't have vaccines for and, you know, we have very little understanding for what the protection is. Yes?

PARTICIPANT: I think it is important to

point out that in vaccine trials those were done in normal individuals and the antibody titers are merely a surrogate for immunity, and it doesn't reflect that the specific immunity and protection to the agent relies only on antibody titers.

DR. SCHIFF: What about the issue of how one would go about adequately selecting samples? This is like a little time capsule that we are setting aside so we can go back and study things in retrospect. Yes?

PARTICIPANT: I wonder, Dr. Scott, if you could answer what is the important scientific question that we are trying to answer with such a repository?

DR. SCOTT: I think one of the things we would like to do is have, in a sense, a surveillance of the products in terms of the antibody levels. For example, we know that measles antibody titers are going down. Well, how do we know that? We know that from our manufacturers to some extent. We also know it from our own serial samples that we used to receive from lot release.

This becomes a problem especially when there is an established titer that must be met and we are being signaled now that it is becoming a problem. So, I think in part for surveillance and we would like to know what the potential for protection is against emerging pathogens. It will not prove that there is protection against these emerging pathogens; I think it will tell us more where we are.

I think also that there are probably a number of other people who would be interested in looking at levels when we see infections that become problematic or more frequent in immune deficient patients to look back and see whether in general there are higher or lower titers, or a great deal of lot-to-lot variation for those products. I think probably the academicians here would also have something to say about whether they think this would be useful or not.

PARTICIPANT: Haven't there been some systems in place? I don't know at what level the screening was done but when people had, for example, pseudomonas immune globulin or CMV, IGIV

with higher titers against CMV, this was not like the BBIG where the patients were specifically immunized, or the tetanus hyperimmune globulins where there is some really small subpopulation that either is known to have a high titer or is specifically immunized and then plasmapheresed. But at least some of the manufacturers must have had systems in place for screening either individual donations or lots and selecting lots based on titers.

DR. SCHIFF: You are right. I mean, you can do screening. You get to the issue of suppose you screen out and you choose all the high H. flu. titers, you can have a very high H. flu. titer but then the rest will decline. So, from a practical standpoint I think it would be very difficult to make hyperimmune sera just out of pooling because then everything else drops.

PARTICIPANT: Yes, but I mean when CMV hyperimmune globulin was being made, was that determined to be hyperimmune at the level of the individual donations or lots?

DR. SCHIFF: That was by pooling individual donors. But you can do that for a few isolated things. If you need CMV; if you needed to

get a pool of high West Nile you could do that. But now you start looking at all the general pathogens and it is just not practical and we have to start thinking about monoclonal spiking. With immunization programs, something that we had discussed, if the actual antibody levels--and Dr. Stiehm alluded to some studies that suggested that antibody titers for H. flu. and pneumococcus are adequate; my sort of sporadic screening suggested that wasn't true but, you know, if it is true then there is no need to immunize donors. But for the things we have vaccines for we could boost the donor pool at least for source plasma where the same donors keep coming back and forth.

We are going to have to move on in a minute. So, let me just bring one other issue out, and that is, is there an interest in forming some subcommittees to try to address these issues? It is one of the questions that Dr. Scott proposed as

part of this meeting. If so, would it be best for people to indicate to you that they would be interested in being on a panel? Not everybody that wants to be, obviously, or can be if we get a large response but the ones that aren't on a panel could be sort of consultants to the panel. I don't know if there is a general show of hands of people that are interested in trying to address these issues. Obviously, we are not going to solve them today but I think we are really just trying to bring up the questions.

DR. SCOTT: I think if there is a need it is important. If there is not a need to identify how we can find out more and potentially make things better for patients, if that need is not perceived or a path towards that is not identified, then it is a different matter.

DR. OCHS: Well, I think this would be a great resource for not only looking at these lots now but retrospectively. I could see that somebody comes up with a very valid functional assay and they could then collect some of these samples to

validate that if we measure antibodies, for instance, with ELISA is this the same as if we use neutralization or a mouse-based assay. So, I can see that over the years this would become a very useful resource for many individuals, not only FDA but out in the community. Of course, one could follow this variation; where does the gamma globulin come from; when was it collected. One could also maybe get some from other countries, from Europe, from Asia. There must be a huge difference between plasma collected in China and plasma collected in Iceland.

DR. SCOTT: Right. I think that is a good point, and the idea that there would be a comparison of products that aren't licensed potentially to ones that are licensed. As you said, it could be very informative, especially under considerations where plasma should and could come from for our own products.

DR. SCHIFF: I think in terms of the issue of these other questions of antibody titers in patients, trough levels versus peak levels--I mean,

how are we going to address this? Are we going to get the answers or are we going to come back in ten years and have this same discussion? I have a feeling we had a similar discussion probably ten years ago. I used to have a slide that said, "this has all been said before but because nobody listened it all must be said again." So, you know, I would like to be able to come back in five years and say that we have some answers and, in that regard we can talk over lunch about forming some groups and, you know, maybe there isn't a good way to approach this and we will just keep bumbling around in the dark and just raising antibody doses until somebody gets better. But I think we really should find a way to address these questions.

Let me turn this back over to you so we can go on to the safety aspects.

DR. SCOTT: I want to thank the panel, and thank you very much for leading the discussion. We are going to go forward to adverse event topics and IGIV safety, and the first speaker will be Dr. Gelfand.

II. Topics in IGIV Safety

Safety and IGIV Product Differences

DR. GELFAND: Thank you, Dr. Scott. It is

a pleasure to be here and I appreciate the invitation. It must be an important meeting because I see a lot of suits in the audience so there must be a lot of company representation. I am reminded by the story of why do doctors dress so poorly, and that is because drug reps don't give out suits.

[Laughter]

Well, it is interesting to hear the discussion because a lot of us have been around immune globulin replacement for a long time. I was Charles Janeway's last Fellow and I remember in 1968 going to the clinic and being told there is a patient there with hypogammaglobulinemia; give him his gamma globulin. I was always used to gamma globulin as being at 1-2 cc injection in the butt. I ask how many of you have 1-2 cc of gamma globulin in your butt as protection? How many went back a second time? Right? And there we were,

administering 50 cc, 60 cc and 70 cc intramuscularly to these patients.

Then in 1969 I did my first intravenous gamma globulin infusion. So, this was 1969. We would strap the patients to a gurney because they were shaking so much; and the half-life I think was over before the infusion was over.

[Laughter]

So, we have come a long way since those early infusions. I calculated last year I probably have done about 25,000 IGIV infusions over the last 35 years and the same questions, as Richard alluded to, persist today.

My topic is to talk about safety and IGIV product differences. I think a lot of the aspects came up during the discussion and sometimes you kick yourself and say I should have put that slide in, but my talk is really to focus on the comparison of currently available products and really to discuss the issue of do the differences in these products impact clinical outcomes. We know that these products differ considerably, and

what I would like to do is very briefly address the whole, overall issue of safety, adverse events, tolerability and a little bit on efficacy.

My sort of comprehensive approach to IGIV safety is to think about the safety in terms of viral inactivation and virus removal; tolerability; incidence of adverse events; and, clearly, efficacy is part of the overall paradigm, if you will, that leads to a concept of safety. In fact, we have had tremendous advancements over the last several decades. In terms of safety, we have introduced new standards, both here and abroad, in terms of conditions that have to be met to ensure, as much as possible, the inadvertent transmission of viruses. We talk about adding methods of virus inactivation and removal that are complementary to even increase margins of safety.

Tolerability--we have seen our infusions go down in terms of the time required from the very lengthy and burdensome infusions to much shorter infusions.

We have seen an advancement in the

incidence of adverse events with the progression of the products that certainly in PID at customary doses of 400-600 mg/kg have a very low incidence of adverse events, much lower and much different than the severe adverse events that occurred with some of the higher doses for autoimmune and inflammatory diseases, and you will hear more about that. Interestingly, when we try to look at adverse events amongst the products--and I will come back to that, there are virtually no head-to-head comparisons and there are marked differences in the reporting methods.

In terms of efficacy, we have seen a progressive improvement in infection prophylaxis. And, one of the aspects, just because some of the data were available, if we look at the initial intramuscular preps, the IGIV preps, solvent detergent and newer preps, we have seen a progressive decrease in the incidence of infections. As I alluded to in my comment during the panel discussion, some of this is clearly attributable to increased dosing; probably

increased ability to deliver some vital antibodies; but, again, the higher doses may allow us to take advantage of some of the non-antibody-mediated effects of intravenous gamma globulins that have been extensively studied in immune and inflammatory diseases.

I did mention to Richard that I think part of the issue with the higher doses--and I will come back to that when we talk about peaks and troughs and what they mean--I certainly think we have to drive gamma globulin into tissues, certainly along mucosal surfaces and sinopulmonary area or other parts to be effective. In fact, by driving these peaks into those tissues, they may not be subject to the same catabolic phenomena that serum IgG undergoes with catabolism. We know from antibody studies that have been done, cytotoxic antibodies treating various diseases, in tissues the half-lives may be much longer than IgG half-lives in the serum. So, to me, there still is an issue of whether we need a good peak or a good trough.

Now, one of the interesting aspects about

safety--and Becky alluded to this--is that when you look at the Immune Deficiency Foundation survey and you look at the patients in a household with a primary immune deficiency disease, it is rather striking for those of us who grew up with the idea that this is a childhood disease, congenital disease in the first few years of life but you can see that more than half of the patients are, in fact, above the age of 18. More strikingly, if you look at the current IGIV users by age--remember, these are the primary immune deficiencies, not neurologic disease or dermatologic disease where they tend to be older, these are PID patients--look at the percentage of patients that are above 18. In fact, 8 percent of the patients, during the survey, that were on IGIV were 65 years or older.

So, I think from a safety point of view it sort of poses a number of challenges for us. So, the number of PID patients requiring Ig replacement has increased over the last decade but, importantly, the average age of the patients receiving replacement therapy has really increased

dramatically.

From a safety point of view, it poses new challenges for us. We now have to deal with many more co-morbid diseases than we dealt with in children who were on replacement, and considerations of fluid volume, salt load, sugar load and tolerability overall become important issues, particularly with the older patients who may have associated diseases.

We will hear more about this but, very briefly, if we look at the IDF survey and symptoms following infusion, you can see that headache was the predominant one, fever, nausea, cough, sore throat, shortness of breath, fainting and "blank." I don't know if the patients went blank or the survey went blank but somebody went blank.

[Laughter]

If we look at why patients avoid specific products, far and away the largest reason for patients wanting to avoid products or infusions overall is, from the survey, the side effects themselves.

So, what about adverse events? Well, there certainly are major limitations of trying to compare clinical trial data and adverse event data.

I think, again, when we talk, for example, about efficacy, we do licensing trials or we hear about licensing trials. They are not truly efficacy trials. To me, an efficacy trial to determine if there are true differences in efficacy is to take patients with active disease or chronic disease such as bronchiectasis and determine if the long-term outcome a year or two later is impacted by Ig replacement. Most of the data that we have for efficacy and certainly for adverse events are from licensing studies.

They are certainly not head-to-head. The only times they may be head-to-head is when a new product replaces an old one within the same company. The study methodology differs considerably. Recommendations change from the FDA, and so on, for how to do this. And, there are also various differences as things evolve with the instructions for how the principal investigator

should monitor AEs. Patient selection is not random. There are many exclusions. In fact, I often think it is the patients who have an adverse event or history of adverse events in whom you would like to see what a new product would do but, in fact, patients who had adverse events are generally excluded from these studies. There are few patients who may have many AEs in some of these studies. On the other hand, there may be a lot of patients who have very few AEs and it is hard to discern from some of these package inserts what type of data were collected.

Again, a busy slide but only to tell you that side effect profiles are generally quite common. Interestingly, if you look at the adverse event rate overall in these studies in PID, the percentage or the incidence or prevalence of adverse events is relatively consistent and relatively low, between 5-10 percent, but the size of these trials really is quite small. There is a larger trial here, as Richard alluded to, but there really is a relatively small number of infusions

overall so it is hard to look at package insert data in terms of the incidence of adverse events.

We know, and we will hear more, that product features per se can affect clinical tolerability and the incidence of adverse events. We know that volume load, osmolality, sodium content, sugar content, and much less so pH and IgA content can influence clinical tolerability and the prevalence of adverse events.

Again I apologize for this busy slide but it is in your handout. I just want to show you how these products differ looking at the currently licensed products and taking you through various parameters. So, the first parameter is the formulation, lyophilized versus liquid. If we look at the available concentrations--and Hans alluded to it--they vary considerably, from 3 percent up to currently available products that may be up to 12 percent. Well, this concentration really dictates the volume that has to be administered for a given dose. As we do more replacement and consider it regardless of the route of administration, the

concentration has a major impact on the volume load.

If we look at other aspects in terms of the infusion rates, infusion rates vary all across the map from infusions for a standard dose taking upwards of 8 hours to others that can be completed in 60-90 minutes. A lot of this is dictated by what the content of some of the materials are. You heard that there are products that contain various sugars. There are some products that don't have any sugar whatsoever; glycine is used. The sodium content varies quite remarkably. And, this has a bearing then on how, for example, lyophilized preparations may be made up because in the lyophilized preparations there are fixed concentrations of sugar and salt and, obviously, the more concentrated that solution may be the higher the osmolarity since sugar and salt are the major determinants of osmolarity in these products. Again, the osmolarity can also vary. Finally, pH and IgA content also can vary significantly.

So, overall if we look at these products

they differ considerably in a number of different aspects. The real issue for me when I look at this is how does this dictate what the clinical outcome may be? How do we talk about these different products and make a selection based on tolerability, adverse events and ultimately even efficacy?

I want to turn finally to the routes of administration because that sets up I think the discussion from a safety point of view and also this afternoon's discussion. There are different pros and cons to the routes of administration. I think that, as you heard and as I think was alluded to during the earlier discussion, subcutaneous infusions are essentially unsupervised; intravenous preparations are generally supervised. Compliance is not assured with subcutaneous; it is assured with the intravenous.

I am always reminded, taking care of patients with not only immune deficiency but with asthma and the high cost of medications and co-pays, with our asthma patients over and over

again we see that patients are given a 30-day prescription and what they do is they take their medicine every second day or every third day to prolong the prescription and have less financial burden. I think we are also starting to see some issues related to compliance when it is unsupervised. Follow-up is less regular. There is a certain freedom that patients enjoy. There is group support with the intravenous.

I think there are other issues that are important to consider. There are time effects. And, I think the real critical question in this whole controversy about what is best is what does a steady trough do versus a peak-to-trough variability? And, how important is the trough level, as we discussed in the last panel discussion, versus how important is the peak? And, there are just some other aspects in terms of adverse events and so on. I think there are few, if any, systemic adverse events with subcutaneous but I think the new preparations really have a very low incidence of systemic adverse events and for

the vast majority of patients this is not a deterrent because the incidence is so low. I don't want to dwell on the pharmacoeconomics or other issues that bear on some of these decisions.

To me, the ideal intravenous immunoglobulin is a liquid that is ready to use with a high concentration, 10 percent or higher; a low incidence of adverse events and that has good tolerability. Importantly, particularly in terms of efficacy, I think you heard that efficacy comparisons have been few and far between, not head-to-head, and most of them are derived from licensing trials and I don't think there is really any significant apparent difference that has been defined between products in terms of efficacy when we look at standard outcomes. I never understood how one could define sinusitis as an acute episode or a chronic episode in PID patients because it is such a common aspect.

Efficacy is also defined by the elimination of organisms, and I come back to the issue of mycoplasma which certainly in my

experience over the last 20-plus years when we first defined mycoplasma as the major culprit in chronic sinopulmonary disease, as well as acute infections in other sites--these are organisms that are very low grade pathogens. They are insidious. But, more importantly, they don't respond to any of the conventional antibiotics that are used against H. flu. or S. pneumoniae. In fact, because they are so difficult to isolate in patients who do not respond to the anti-pneumo. or H. flu. types of antibiotics at least in our institution, and I know in a number of others, the treatment for mycoplasma for example with a tetracycline-like or maybe some of the floxacillins now is really what is necessary to limit some of the disease.

It is hard to know what efficacy as a definition is going to be. Is it going to be prevention of infection? Is it going to be prevention of infection but an arrest of progression of disease? I think for the patients with PID who have established disease, particularly chronic sinopulmonary disease, we need to assure

ourselves that we are choosing the best product that can arrest the progression of the disease and perhaps allow repair of the lung.

Just a last thing, which has been something of interest to us in my unit is, you know, the old-fashioned way, particularly when we have lyophilized preps was when the patient would arrive. We would notify the pharmacy because we wouldn't make up the product until we knew the patient was coming. It was prepared and delivered to the infusion site and started, and often we used the concentrations that were lower, with defined infusion rates, and you can see that for a standard infusion for this particular patient it might take upwards of 5 hours. I think with newer preparations today the patient arrives; it is prepared on site and it is much shorter in terms of the prep time. Even just following package insert guidelines, one can give a 10 percent solution at this rate which is virtually the replacement dose for that patient, close to 500 mg/kg, in an hour. This is not rapid infusion; this is the package

insert approved rate which the vast majority, if not all of our patients, tolerate, making it a much shorter infusion.

So, let me conclude then by saying that Ig replacement is a life-saving medication in patients with PID. There have been significant advances in Ig replacement therapy. Ig replacement is generally a safe mode of therapy. There are some concerns that linger regardless of the route of administration. And, patients now have options as to the route of administration, and the subcutaneous option is currently not licensed but is under investigation and I am sure will be approved soon. So, thank you very much. Is there time for questions?

DR. PIERCE: Dr. Pierce, FDA. You alluded to the potential for the future of evaluating not only prevention of infections but also addressing whether there is a change in the long-term clinical course for people with chronic infectious processes like bronchiectasis and chronic sinopulmonary infections. Do you think that exploring doing

serial studies over time in subjects with MRIs of the sinuses, for example, would hold some promise? I mean, do we have anecdotal evidence of people who with a more aggressive regimen for example have actually shown a trend towards improvement?

DR. GELFAND: Right, I will just tell you our policy which does take advantage of using CTs, particularly of the sinuses and, very importantly, of the chest. As you heard earlier, doing pulmonary function studies, even the total body box system really only picks up patients after they drop over the cliff. Certainly, if there is an impairment of pulmonary function body box measurements are good longitudinal measurements to follow for obstructive or restrictive disease. But the important thing in doing CTs is you can measure mucosal thickening; you can look at opacification. And, in the chest, now with the high resolution CTs, you can actually look at airway wall thickening. You can look at the size of the bronchiectatic patches. It is interesting, you know, cystic fibrosis develops saccular

bronchiectasis. Hypogams rarely, if ever, develop saccular bronchiectasis; they have cylindrical bronchiectasis. So, you can actually measure the segments on high resolution CT to look at the cylindrical piece and see if there is resolution. So, there are ways to do long-term follow-ups in a longitudinal way with high resolution CT scans.

Safety of IGIV Therapy Infusion-Related Adverse Events

DR. BALLOW: Thank you for the kind invitation to address this group--I see a lot of friends from various segments of academia and pharmaceutical industry--and discuss some of these issues.

I was asked to address some of the infusion-related adverse events and look at possible mechanisms if we know some of those mechanisms. Let me start off with some of the more common adverse events that are shown on this slide. These are certainly common ones that we all have seen in our patients through the years, particularly with what I call the first several

generations of IGIV products where a lot of these adverse events were much more common. But, in general, they occur to a minor degree 5-10 percent. Most of them are controlled by using premedication. Occasionally they can occur after the infusion at 24, 48 and 72 hours in some of our patients, particularly if they have underlying risk factors. They appear to occur more commonly, at least in the patients with primary immune deficiency disease, in those who have ongoing active infection whether it is sinusitis or bronchiectasis or bronchitis. Although we don't know what the exact mechanism is, it has been postulated that perhaps the antibodies combining with bacterial breakdown products or antigens contribute to some of these adverse events during infusion or shortly thereafter.

In one very large prospective study from Helen Chapel's group, in the U.K., in which they looked at 459 antibody deficiency patients in over 13,000 infusions, they found a very, very low adverse reaction rate of 0.8 percent, as was pointed out by one of the previous speakers. They

broke this down and they had no serious severe adverse events; 0.6 were mild; 0.1 percent were moderate. They saw more adverse events in those that were undergoing home infusion and higher adverse events in those that had active infection, 5.1 percent versus an overall adverse reaction rate of 0.8 percent.

So, they felt that they could avoid a lot of these adverse reactions, particularly those that were on the moderate side, if they would take some additional care in some of the contributory factors like active infection and making sure, for example, those patients were on prophylactics, or maybe delaying for a couple of days IGIV infusion although that is not practical and perhaps not a good idea. We are always forced to give, at least in our shop, IGIV infusion in those patients who come in who have an active infection like sinusitis or bronchitis.

Most or them respond to altering the infusion rate if they are associated with the infusion. For those that occur early on with the

infusion or with medication or premedication, listed up here on this slide, rarely do we have to use corticosteroids. I know some infusion centers use corticosteroids as kind of a prophylactic approach in premedication, and perhaps we could have some further discussion about whether that is really needed or not. We rarely actually have to use it with the new generation products.

As I alluded to before as far as the mechanism of these mild adverse events, antigen antibody complexes from the bacterial products in those that have ongoing active inflammation or infection, perhaps activation of complement due to small aggregates that occur during the infusion, but there are very little studies of what happens with the actual infusions with regard to the production of aggregates, dimers, trimers and actual aggregates. Some of these studies were done a number of years, 10 or 15 years, ago but I haven't seen anything recently and perhaps, depending on the underlying risk factor of the patient, the nature of the patient and the age of

the patient, etc., you know, these risk factors might produce more aggregates as the products are being infused and cause complement activation and adverse reactions.

Of course, there is the possibility of vasoactive proteins in IGIV as contaminants and there have been a couple of papers to suggest that there might be a correlation here but, again, we have very limited information. There is tremendous product variability, and particularly with the changes in how products are manufactured there are going to be marked differences across products with regard to some of these vasoactive contaminants.

Reactions related to IgA in IGIV--that is always a topic that comes up in a variety of forums and, of course, there could be either anaphylactic or anaphylactoid events, as Dr. Buckley published in The New England Journal of Medicine a number of years ago where they reported several patients who had true anaphylactic IgE antibody reactions against the IgA in the product and subsequently went on to tolerate their infusions by using a

product that had low concentrations of IgA. But in actuality, I think from kind of an informal discussion with my colleagues, this anaphylactic reaction is probably very rare and unusual. Unfortunately, we have no mechanism for testing our patients since the previous source for measuring IgE antibody antibodies to IgA is not available anymore.

Well, what about IgG antibodies to IgA? Charlotte Cunningham-Rundles has published a paper, as well as others, to show that, indeed, patients such as with common and variable immunodeficiencies do have IgG antibodies to IgA, 10-22 percent. Other studies have shown an even higher proportion of patients with IgG antibodies to IgA, but a number of these studies really show no correlation at all between these IgG antibodies to IgA as far at least as severe reactions. Again, they appear to be rather uncommon from the data of Cunningham-Rundles.

This slide which is supposed to show the IgA contents of the various products didn't come

through on the e-mail, unfortunately, but I think most of you realize, from Dr. Gelfand's table that he showed you in his presentation, that there is tremendous variability in the IgA content between different products. So, if there is a consideration that you are worried about an anaphylactic reaction or anaphylactoid reaction there are choices in products.

Renal adverse events--this is where surveillance certainly paid off with the MedWatch program of the FDA in which they informed us that there were these very serious renal adverse events that were primarily reported in patients who were getting very high doses of IGIV because they had underlying hematopoietic or autoimmune neurologic disorders. The patient population was quite different than those with primary immune deficiency disease. They had a much higher median age. Their reactions usually occurred within 7 days of the IGIV administration, so not sort of immediately with the infusion process or 24 hours thereafter as we usually see with some of the other adverse

events. Most important, they had preexisting underlying contributory factors such as renal disease, diabetes, dehydration and perhaps medication that could contribute to the nephrotoxicity.

The mechanism is thought to be osmotic damage from the sugars that were contained as stabilizers in the IGIV, and 90 percent of these adverse events were associated with products that contained sucrose. Hopefully, we will see this adverse event go away as most of the newer products that we are now seeing either in trial or recently approved do not have sugars as stabilizers but use amino acids as well, but that remains to be seen.

Aseptic meningitis--we have all experienced this, particularly in those patients to whom we are giving much higher doses of gamma globulin either as replacement therapy to gain a higher trough level or certainly in patients with autoimmune disease. This is data that was published by Dalakas at NIH in patients with neuromuscular autoimmune disease, in which they saw

an incidence of about 11 percent, and who had all the symptoms and signs of aseptic meningitis as well as CSF that showed some pleocytosis. Migraine seemed to be a predisposing factor.

The problem here is that this remains a very, very difficult adverse event to treat. We all go through the usual types of approaches such as changing the infusion rate, although many of these occur near the end of the infusion and certainly at the higher infusion rates or changing products; premedication with Tylenol or NSAIDS or giving steroids or Imitrex because of the prior history of many of these patients of migraine headaches. So, none of these approaches is entirely satisfactory. It is kind of individualized to the patients themselves whether it is successful or not. The mechanism is not quite clear. Undoubtedly, in those patients with autoimmune disease it is related to the high protein load crossing the CSF barrier.

Much more disturbing are the cardiovascular adverse events, and I want to spend

a little bit of time on this because there is a little bit of controversy about what the possible or potential mechanisms are. Let me just state briefly that there have been a couple of reports of arrhythmias in a variety of settings and very, very unusual adverse events but, nevertheless, they have been reported and they are out there.

Much more disturbing, of course, are the thromboembolic events leading to myocardial infarction or other target organs such as deep vein thrombosis or retinal vein occlusion, pulmonary embolism, stroke, etc. What are the contributory factors? Well, I think everyone would agree that the underlying patient risk factors are very, very important here, as well as the patient's age. Blood viscosity--and I will come back to this in a little bit more detail; and there has been some issue raised about product osmolarity which is not quite settled with. This is an important component which may be contributing to this type of adverse event in particular to the change in rheology of the blood.

Volume overload and rapid infusion--a lot of these events, as I said, have been witnessed in patients with underlying risk factors and patients

with autoimmune disease and using very high doses of 2 g/kg IGIV, but also rapid infusion.

There has been one paper to suggest that there may be other components of IGIV that contribute to these thromboembolic events, such as procoagulant factors. This is one paper published by Wolberg that showed that there is Factor XI in these products, in which they surveyed 8 different brands, 29 samples, and found levels in 26/29 samples and, certainly, there is a lot of variability in the concentrations of Factor XI among the various brands which they attributed to the manufacturing process itself. Whether this contributes to these thrombotic events in these patients is not clear but certainly could be one factor.

There are numerous, numerous publications in the literature about these thrombotic events representing various target organs, whether stroke

or MI or pulmonary embolism, etc. So, let me just go over one or two of them since we don't have time to look at more than that.

This is a typical paper in the neurology literature, 16 cases of stroke associated with IGIV infusion. Ten patients had neuromuscular disease, 10 had hematologic disease like ITP, 14 occurred within 24 hours of the infusion. Half received 5 percent and the other half received 10 percent. So, I have to assume, although it wasn't stated, that this was a lyophilized preparation but I can't be certain. But you will see that the infusion rate was very high, 300 mL/hour, which perhaps for this risk patient population is too high. Fifty percent occurred with the first infusion; 9 patients had multifocal infarctions; and all but one patient had underlying risk factors. So, this is pretty much what one sees when one looks at a variety of papers which report these thromboembolic events.

But they also occur in patients with primary immune deficiency when they are given

replacement gamma globulin therapy. This is the Iowa group that reports 3 patients with antibody deficiency. All were receiving a lyophilized product that was reconstituted at 10 percent. Again, they used the maximum infusion rate of 300 mL/hour. All of them had underlying risk factors or known vascular disease. So, again, this keeps cropping up so it is clear that we have to select these patients very carefully with regard to perhaps both product and infusion rates, and perhaps other parameters that dictate a difference between products.

Well, what are the mechanisms? I will tell you right off I am not sure what the mechanism is, other than the underlying risk factors that we just talked about. But perhaps viscosity, you know, plays an important role here in these patients. This is again a paper reported by Dalakas in the neurology literature in which they looked at patients that they were infusing with amyotrophic lateral sclerosis and IgM paraproteinemic polyneuropathy, giving very, very

large doses, 2 g/kg. They measured the viscosity in these patients and, as you can see, 3 of the ALS patients and all the patients with this IgM paraprotein exceeded the upper limit for normal serum viscosity, normal being 1.5 and 1.9, and in many of the patients they saw levels obviously higher than this; in some they saw them as high as 2.6. And, it correlated with the serum IgG level, again getting very large amounts of protein.

So, their recommendation is to monitor viscosity, particularly in those with underlying risk factors, as shown on this slide. I have to say that certainly in my primary immune deficiency patients I do not monitor viscosity. I am not sure that neurologists and hematologists monitor viscosity as well.

But in addition to viscosity, the whole concept of rheology--you know, other than the plasma proteins which contribute to the viscosity are the blood elements themselves, such as the platelets and perhaps leukocytes that potentially can contribute to sludging and these thromboembolic

events.

Again, this is an older paper, in Lancet in 1992, and I wasn't able, at least on a brief survey, to come across anything recent but it does suggest, for example, in an ITP patient where you are giving large doses of gamma globulin and you are changing the platelet count very rapidly that could potentially change the blood rheology and contribute to some of these thromboembolic events in these patients.

Vasoactive--others have raised issues about proinflammatory cytokines which have been measured in association with giving IGIV. One paper demonstrated IL-6, IL-8 and TNF-alpha. Another paper demonstrated IL-6 and thromboxane B-2, and you can see the details in your handout. In this study they actually used normal subjects, 500 mg/kg given at various rates, 0.04. 0.06 and 0.08 mL/kg/minute, and showed that at the higher infusion rate 7/8 patients--these were normal subjects, not those with underlying risk factors--had an adverse event and although there

were no changes in some of these mediators and cytokines, such as histamine, tryptase, TNF-alpha or IL-1-beta, there were significant changes in IL-6 and thromboxane B-2. So, again, this suggests that certainly associated with IGIV infusions there could be release of certain mediators, cytokines, etc., that contribute to these thromboembolic events.

The FDA, in August of 2002, came out with an interim statement about this particular adverse event. As I am sure most of you are familiar here, cardiovascular risk factors, advanced age, atherosclerosis, neuromuscular disease, as well as hematologic disease are all risk factors, and I think we all agree with that. There is a question whether rapid infusions above those that are recommended by the package insert of the manufacturers are also a risk factor.

They appeared to occur more frequently in those patients who were getting lyophilized products, particularly those who were getting lyophilized reconstituted at 10 percent

concentration, although I certainly don't have access to all the data that was fed to the FDA to say that these events didn't occur with liquid products as well. I have been told that they have occurred with liquid products but I don't have that information.

Certainly, factors that contribute to hyper-viscosity and underlying risk factors like proteinemia, dehydration, obviously giving a high protein load, and hypercholesteremia, have to contribute to these vasoocclusive events.

They concluded that there was insufficient evidence, at least according to their surveillance, of other components in the IGIV such as sugars or sodium content that may contribute to the osmolality or other components that may be contributing to these thromboembolic events, and I am anxious to hear any follow-up from their perspective.

We don't have time to talk about some of the other adverse events that have been associated with IGIV infusions. Some are found more immediate

with infusion; some are more delayed, such as was mentioned I think by one of the previous speakers; potentially hemolytic reactions due to isogglutinans in the IGIV. But we don't have time to talk about these, and most of them are very, very rare and I certainly haven't seen them. Progressive neurodegeneration was also mentioned previously and it is something to be aware of.

A trial of 50 subjects has only a statistical power to detect those adverse events that occur with a frequency of greater than 6 percent. I bring that up because most of these trials, except for the Bayer trial, were actually very small trials to look at tolerability, not efficacy but tolerability in comparison with the previous product in which they are using maybe 35, 40 subjects in a clinical trial. So, our clinical trials are not going to probably bring out some of the adverse events that we are all very apprehensive about, like the thromboembolic events, just because of the nature of the patient selection for these trials, as was mentioned I think by Dr.

Gelfand, and also the numbers.

There have been some changes in the guidelines with regard to package insert reporting. They are shown here. Let me come back to this in the next slide.

I took a look at the package insert and tried to kind of get an appreciation for these adverse events as a clinician who wants to try to get an idea of products selection vis-a-vis these potential adverse events in my patients.

So, this is the primary immune deficiency disease. This is in patients with ITP. Most of the data is in primary immune deficiency disease because that is where the clinical trials have occurred. This is the percent of the products. You can see this is a lyophilized product that can be reconstituted as 5 percent or 10 percent. According to the package insert, there is 6 percent of severe adverse events with the 5 percent, 10.5 with the 10 percent. These are all liquid products. All these are the newer generation products that have been approved in the past year,

5 percent, 5 percent and 10 percent. You can see that the severe adverse events are somewhat less than with the lyophilized products but, nevertheless, in the same ball park. In moderate adverse events you can see tremendous variability, 26 percent, 1.5 percent and 34 percent. Even looking at headache, 15 percent, 53 percent and 8 percent.

So, there is quite a variability in the package inserts. I think as a clinician I would have a difficult time perhaps trying to pick out a product that might be suitable for a patient. There is really very little information in the package insert that actually describes what they mean by mild adverse events, moderate adverse events and severe adverse events, and that might be something that might be useful for a clinician in trying to understand some of these data on the adverse events in the package inserts.

Here are some recommendations that I actually adapted from another paper, published in Transfusion Medicine in 2003: Revisit the

ascertainment of data to be able to put some additional information in the package insert to help clinicians with regard to this area. Compare tolerability between products for a patient group or diagnosis. Most of the studies, obviously, are done with patients with primary immune deficiency disease or patients with ITP. There has really only been one study that has actually looked across products as far as comparison in tolerability. There have been a few other papers in the literature that go back to, I guess, the '80s and many of those products are probably not on the market today. So, that would certainly be useful but may be impractical.

Improved data collection and criteria for these adverse events, particularly as they pertain to trying to inform the clinician or medication provider to have an informed decision. Each product may have a unique tolerability and safety profile, as was alluded to by Dr. Gelfand in his presentation. Clearly, there are manufacturing differences. There are differences in the type of

stabilizers that are being used and other manufacturing differences as well. Though it may not be practical to have a head-to-head comparison, I think all of us would agree that that certainly would be valuable if it were available.

Surveillance and registries--I think we saw an advance certainly with the renal adverse events related to sucrose-containing products. One of the things that we might talk about is ways of enhancing surveillance or even coming up with registries. I know the IDF was interested in this a few years ago to be able to develop a more comprehensive surveillance registry system to try to identify some of these newer adverse events and get this information back to clinicians as fast as possible, and also to be able to understand what the risk factors and perhaps what the mechanisms are. I think I will stop there, and thank you very much.

DR. SCOTT: We are running behind time so I think we will go on to the next speaker and we will take a 45-minute lunch instead of a one-hour

lunch. There is a cafeteria in this building. So, welcome to Don Baker. Thank you.

An Emerging Issue with IGIV Products

DR. BAKER: Well, I am acutely aware that I am the last speaker before lunch and what I would like to be able to promise you is a crisp, insightful and killer presentation that makes your attendance at this conference worthwhile. Unfortunately, sadly, this will not be that presentation.

[Laughter]

But what I can promise you is that if you solve the problem that I am going to present here the industry will be very grateful. The problem I am going to describe is the most vexing problem that manufacturers have right now in the production of immune globulins, and also I will personally contribute a fine bottle of California wine, white or red, your preference, because my boss has assured me that if I have a third event this year of one of these recalls associated with this event I can start polishing up my resume. So, I have

personal incentive to bring this to a conclusion.

What are we talking about? Urticaria and pruritus, or hives and itching to most of us. This is an adverse event which is rare but common, if you like, with IGIVs. It is a common rare event. Typically, manufacturers receive 0-3 reports of urticaria and pruritus per lot of IGIV manufactured. Over the last few years virtually every manufacturer--I think it is probably every but I will say "virtually"--has had one or more lots of IGIV for which they have had an exceptional frequency of these kind of events and this has led to removal of the associated product from distribution, and a lot of intense conversations with the FDA.

These events are not life-threatening and I should say it has not been our experience that these events have progressed to life-threatening events. Obviously, if you are the patient you still don't appreciate it but at least your life is not in danger.

For us, up until about June of last year I

was feeling pretty smug about this because we had not had any of these events and, therefore, we clearly had a superior product. Unfortunately, we had our first event in June of last year and this is what I am going to refer to through the presentation as withdrawal #1. That is U.S. #1. About 6 months later we had a second event. The first one was only distributed in Europe. This is going to be #2, Europe, #2. These events are what I am going to discuss today and some of the investigations that we undertook into them.

As I said, what is the concern over all of this? Well, the concern over all of this is that these events could progress to something that would be life-threatening but, again, that has not yet been our experience.

When you see an increase in the frequency of an adverse event from spontaneous reports, and an adverse event that is known to occur, one of the first things you have to wonder about is, is this real because there are all kinds of reporting biases in spontaneous event reports and any kind of

frequency determination from spontaneous reports is inherently and perhaps fatally flawed. Of course, as statisticians remind me all the time, random events cluster randomly. So, how do we know that what we are seeing just isn't a random cluster of events that would normally occur?

Well, I would say for most of the manufacturers that I have talked to about this the events were seen not in patients who were new to IGIV therapy. Typically, these are patients who have been treated uneventfully for years. There wasn't an associated change in product, or dose, or infusion rates. And, in one instance we had a similar allergic reaction on rechallenge. In other words, one of the patients received the same lot--not deliberately, I should say as that was a little pharmacy error--and had the same event. So, that would argue against random events because at least it seems to be predictable. Of course, in light of this kind of observation, we do have to take action just in abundance of caution.

The second thing you might wonder is are

these events generally increasing with IGIV? In other words, are manufacturers reacting to a sort of generally increasing trend? Probably the data is less clear. I don't think so. We went back and took a look at our PSURs on our product and over the last 4 years analyzed it for hives, itching, rash, the sort of events that you would see, and there was an increase in product distribution over that time so, net-net, I don't think so. I don't think we are seeing a general increase in these kinds of events.

How would you signal one of these kinds of events? How would you tell this from a normal, if you like random U/P event? This is the abbreviated case report form, our index case and our withdrawal #1. This is very, very typical of the kind of event when you see it. This was CVID. They had received our product for 7 years so it is on a monthly basis. They had very extensive exposure. The event occurs relatively rapidly, either during the course of the infusion or very, very shortly thereafter, and it is not a local reaction. You

see hives in all the usual places. Again, the event typically spontaneously resolves within 24 hours with or without intervention.

So, that is not really very helpful as a presentation. However, I think any of you that are physicians that are treating these kinds of patients, when you do have a situation in which you get urticaria for a patient that has a significant long-term exposure to the same product, that should at least alert you to that possibility.

For the manufacturer and the timing of the reports, what happens when you have one of these situations is that you get the cases typically coming in fast and furious in your reports. For this first one we had 18 reports. Although we had made the decision to recall when we got number 9, there is a delay in reporting so during that time period, just a little under a month, we had received 18 reports. So, that was a very significant departure from normality for a manufacturer.

The distribution of events--one of the

things that you need to be careful about as a manufacturer when you look at this is to make sure that you are not getting some biased reporting from a single institution or a small local group of institutions. That often reflects either something unusual about practice in that place or some reporting bias from that institution. As you can see, for our first withdrawal we got reports from all over. Basically it followed the distribution of the product. There was no single institution which accounted for the predominance of the reports.

For the European event, again, we saw events from two different countries. The European report had fewer events associated with it and there was a component in France of active surveillance. Once they started to get a few, the French authorities actually started calling around and asking if people had seen that event. So, that one is a little softer, however, the number of events and the presentation is typical of what we have seen.

Investigations--again, I am a quality guy, which clearly shows, and I approach this from a quality assurance perspective. Quality people have

a number of tools that they use to look into problems, and one of them is the fish-bone diagram. This is where we try to bucket the various potential root causes for an event that we have seen. It is a truism in the quality assurance mode that root causes for a problem rarely travel alone so we try to divide them up into the various buckets and look at them. So, here we have product, procedure, patient and a bucket that I call psychosocial. That takes in all of those things such as external stress on the patient, maybe there is a very stressful environment when the infusion is administered; geography; local cultures, whatever, that might impact an event.

This is just a summary of the characteristics of withdrawal #1, product, number of vials. The key thing that I want to point in that is that even though these kinds of events are probably under-reported, we got one report for what

I call every 22 doses administered and that is assuming a 50 g dose, which is high but I was trying to be relatively conservative on this. What this suggests is that this event does not occur in all patients exposed to the product. Again, that is consistent with other manufacturers so that, obviously, suggests a patient factor and I am going to come to that later. Withdrawal #2, the same sort of thing, reports in the same sort of order of magnitude of number of reports per dose.

I am not going to go into our manufacturing process but just to indicate that the manufacturing of our product takes place in two facilities, one in Los Angeles in which Fraction II is prepared, and one in Belgium where Fraction II is processed into IGIV. The reason I am mentioning that is because that gives us the opportunity to review very, very complex batch records.

In terms of potential product factors, for the associated lots the release testing was absolutely unremarkable. The parameters were not even at the extremes of the normal product. The

subset of release tests was repeated on lots that came back from the field and that was to address issues, and these were lots that actually came from clinics that reported these adverse events. This was to address had something happened to the product during the distribution process or with time and, again, the values were the same and unremarkable.

I am not going to go into the selected test results, just to give a flavor of the kinds of things that we do look at.

Additional testing--we did some extensive electrophoretic analysis which was again unremarkable. We worked with a colleague of ours, Dr. Romberg at ZLB Behring, to take a look at PKA on standing. What we were trying to address here was if there had been some delay in the administration of a product--you know, if the product was pooled, makeup in the infusion bad, and the patient didn't show up or there was some delay in infusion, could that have led to increase in PKA that could have led to this kind of a problem. The

answer was no.

I mentioned the complex batch records. We put a team on these and went through all of the batch record review. There was absolutely nothing of significance, not even in terms of in-process parameters. We looked to see whether some in-process parameters might have been at the extremes of the range. This was uninformative.

We also took a look at environment issues, and bioburden issues and excursions because one of the hypotheses that we looked at was if there was contamination with some unusual microbial contaminant of the process stream. The answer again was no, there were no unusual bioburden issues and again that was not helpful. We took a look at the albumin stabilizer. There is albumin in this product. Again, the albumin stabilizer was used in many other lots and there was nothing unusual there. Ditto for the vial stoppers and ancillary devices. These were shared with many lots and, again, no association. And, there were no temperature excursions for any of these products

during the distribution. So, again, entirely unhelpful.

We also took a look at sister lots. The only lot that had a sister lot, that is, a lot that shared some component of the Fraction II was our lot withdrawal #1. There were no adverse event reports on the sister lot.

We looked at preceding and successor lots, the thought process here being that if there was something going on in the manufacturing process it could have been signaled either by adverse events in the preceding lots at an unusual frequency or in the successor lots, those manufactured afterwards. We typically run 3 or 4 lots a week so there is a relatively close temporal association in the manufacture of these lots and, again, I don't think there was anything associated with the preceding or successor lots.

Raw material, potential product factors--both of these lots were manufactured from U.S. source plasma. However, other manufacturers have reported the same kind of thing from products

prepared from recovered plasma. So, that is not a clear causative factor. The donor counts were similar. Those donor counts are pretty standard for all our lots.

The plasma collection dates--I just want to take a moment here--bleed dates for a given product may cover a fairly extensive range but that is typically because some small portion of the plasma gets hung up--maybe a center is being licensed; maybe there is some paperwork issue so, for example, for lot #1 there was some plasma that had actually been collected in April, 2003. However, the majority of plasma--manufacturers work very hard to keep their plasma inventories as low as possible and the majority of plasma is typically collected within about 3 months of the last plasma date. So, for #1 you would expect that the majority of the plasma was collected in the October, November, December period. For #2 you would expect the majority to be collected in the April, May, June period of 2004. So, you can see there isn't even an overlap in the plasma

collection periods in the majority of them. There is some overlap in collection centers and donors for these 2 lots, and this is an area that we are still exploring but so far that has not pointed to any causative factor.

In terms of looking at adverse events, it has been my experience that it is rare that sort of a random, blind search gets you to a root cause. You usually have to have some kind of hypothesis that you are pursuing and do your analysis in light of the hypothesis. Since the skin appeared to be the target organ for these adverse reactions, then taking a look at the impact of this product on human mast cells seemed like a good thing for us and we contracted these studies out to Dr. Schwartz, at the Medical College of Virginia. I am not going to describe these assays. This is something that we just got recently and the last time I was in the lab was about 15 years ago so I am not even going to try to pretend to know what is going on.

The first was a degranulation assay with

mast cells. The withdrawn lot is 030AA. As you can see, it was not differentiable from controls. Ditto with respect to the binding of IGIV to mast cells. Again, our lot 030AA was not differentiable from controls. And, the detection of anti-IgE in IGIV was also not differentiable from controls.

So, the bottom line is that these experiments did not reveal an autoimmune-type mechanism where the IGIV preparations directly activated the mast cells, and the most telling point in that is if mast cell activation with skin isn't involved in these clinical reactions, there must be patient-specific factors, which I think we all agreed given that all patients did not uniformly react with this adverse event.

So, we took a look, obviously concurrently, at all the potential patient factors--gender, age, treatment indication, concomitant medications, allergies, everything that we could possibly tease out of the reports of these adverse events. The bottom line of that again was absolutely uninformative. The patients actually

were relatively good patients by and large. I think in the first withdrawal something like only 4 of the 18 patients who had described the reaction had indicated that they had any kind of coexisting allergies. They were, by and large, a population that was not premedicated or only had your standard Tylenol, Benadryl type of medication. So, again, it was uninformative. The age covered the full spectrum. And, between the two recalls there wasn't even comparability in terms of the major treatment indication, gender bias or anything. So, this evaluate so far is still in progress but it has been, again, entirely uninformative.

So, next steps--and this is where I am looking for help. I think what we can say is that this is clearly associated with specific product lots. I owe a terminology to Dr. Dash, of PPL, and he refers to these as road blocks and I like that. These road blocks appear episodically. The manufacturing process doesn't appear to be differentiable. There is apparently some sort of patient factor. There doesn't seem to be a

treatment or procedure factor associated with this. And, that is about it from my insight. Thank you very much for your attention and, as I say, there is a good bottle of California wine on the table for anyone who can provide me with a solution. Thank you.

DR. OCHS: I have a question. Is this a bottle of wine for every step?

[Laughter]

DR. BALLOW: I will tell you, with my bonus at risk which is not necessarily large, I would even extend it to two bottles of wine.

DR. OCHS: So, the first step for one bottle of wine would be have you tested--and I would suggest it--have you tested this material by intradermal injection into normal individuals and in some of the patients who reacted?

DR. BALLOW: You know, the answer to the first is no, but I want to give you a little perspective on that. These are for the patient relatively mild adverse events. Dr. Schiff may want to expand on this but approaching clinicians

and saying, "you know, we've got a problem lot here, do you mind if we inject some of this into your patients to see if we can figure out what the problem is?" This is not something that at least our physicians have greeted with cries of joy, or the patients either. I don't know, Richard, if you want to expand on that.

DR. SCHIFF: [Not at microphone; inaudible]...we had a hard time even getting the information we did out of them to try and get all these other factors. I think it is a good idea. We have talked about it. They have very little background [inaudible]...about these products and obviously there may be [inaudible]...

DR. SCOTT: I think Dr. Dash has something to say. DR. DASH: Thanks. Yes, I would like to add to that because we have had a similar problem and I would not take any exception at all to what Don has said and how he has described the reactions. But we have tested I think two or three reacting patients by intradermal and skin prick testing. We used the "rogue lot"

that the individual patient responded to and we also used some "non-rogue" lots that the patient had not bee exposed to. The bottom line is nothing reacted at all except the positive histamine control.

DR. BALLOW: Just to add [not at microphone; inaudible]... unless you test them very soon after the reaction because they [inaudible]... the batch again or subsequently. What we find is [inaudible]... very soon after the reaction because it is not like [inaudible]...but, more importantly, it sounds like some of these patients have armed their mast cells perhaps with IgG to Fc gamma receptors with some additional complexes and they fire and they don't fire again afterwards. So, I think downstream testing is going to be universally negative. Yet, in order to find this it has to be I think very soon after the reaction because their mast cells will have turned over. Most of these things had a primer.

PARTICIPANT: Of course, there is no test that you would know would respond to the patient's

serum or plasma if it was collected the next day, or something. But my suggestion to you would be to take the patient's serum or plasma and mix it with the product in the kind of assay that Dr. Schwartz did. But the question we should ask ourselves as a group is whether we should quickly collect serum or plasma any time we get a patient who has such a reaction and at least have it at minus 80 some place. So, I think we should be partners in trying to understand this, and in order to try to have any chance of capturing something that is happening to the patient at that time, we should try to get serum or plasma from the patient shortly thereafter.

DR. BAKER: You know, I couldn't agree more and getting at this root cause is probably going to be beyond the sole ability of the manufacturer because it is really you guys that are out there that have access to these patients in that critical window of opportunity. So, clearly, anything that you guys can do to help us would be very, very gratefully received.

DR. OCHS: I have an anecdotal comment. This happened to Alpha some 15 years ago. One of our colleagues, very motivated, took the material

and injected himself and he had a whopping reaction. They made the same attempts to find a reason for this and they thought they had a reason. I wonder if you did this, they looked at the lot of Cohn Fraction II which had I think 2 colony-forming cells below the upper limit of normal, namely, 648 instead of 650. That material was sent to Japan. Japan said, no, we are tourists; we don't take it, and they shipped it back to the United States and that lot, with this high colony count of bacteria just two notches below the upper limit, was processed and caused this problem. So, they did not figure out what it was but it was one unusual and outstanding difference between the regular lots of Cohn Fraction II and this particular one. So the idea there was that they had something from these bacteria that may have acted on mast cells or somewhere, endotoxin or who knows what.

DR. BALLOW: Yes, I just want to respond

to that and since Alpha is no longer a viable corporation I can speak pretty candidly. All the manufacturers in that period of '96, '97, '98, with the encouragement of the FDA, were encouraged I guess to clean up their bioburden and their process. There have been dramatic improvements since that and Alpha happened to be one of the ones that had a particular problem there. I can tell you that there is a world of difference between permissible bioburdens now and what was permissible in that period, and it is orders of magnitude different. But, again, you know, clearly that is a potential. What is puzzling for me though after all this effort in cleanup, is why we are now seeing this situation where we have never seen it before. Dr. Scott is trying to kick me and she wants me to release you guys for lunch. So, thank you again for your attention. The offer still stands.

[Luncheon recess.]

A F T E R N O O N P R O C E E D I N G S

DR. SCOTT: In the interest of time, I think we will get started. Just a few announcements. Please fill out, if you have time, your evaluation form, and you can leave it at the desk with Rhonda. Also, I wanted to thank Rhonda and the other people that have helped organize this workshop, and I want to thank everybody so far for your participation. This session is going to be on adverse event surveillance. Because of the time limitations--we have been told we have to try to leave by 5:00--what we are going to do is Dr. Wise will speak for 10 minutes instead of 30. The panel will be for 20 minutes instead of 40. If we get more time in there, we will take it. We will aim for having the break at 3:50 to 4:00 and then finish up from 4:00 to 5:00. Thank you very much. I would like to ask Mrs. Marcia Boyle to give a few words from the Immune Deficiency Foundation, our co-sponsor.

Comments

MS. BOYLE: We don't have many people here

right now; they are probably still eating lunch. We are delighted to be co-sponsoring this workshop with the FDA. Dorothy Scott and Jonathan Goldsmith have put in an incredible amount of time into this.

As you probably know, the focus of the Immune Deficiency Foundation is on the primary immune deficiency diseases. Over 70 percent of the patients that we represent depend on this life-giving preparation, including my son. So, the issues of this workshop are central to our mission and for the last decade we have been spending an incredible amount of our time on the issues of product availability, efficacy and safety, and right now we are in the middle of what I would call a crisis because of reimbursement changes for gamma globulin. Many of our patients are not on Medicare and now it is spreading over so that private payers are not able to get their product. Physicians in private practice and outpatient centers can't infuse it. So, we are concerned that we have this wonderfully safe, efficacious product but also that it is available to the physicians and to the

patients.

So, anyone who has any questions about the efforts of the Immune Deficiency Foundation on this area, please let me know or anyone at the foundation because we are kind of leading the pack on this. Thank you very much.

DR. SCOTT: Thank you. I think we will begin with Bob Wise who is going to talk about the FDA methods of surveillance; what we have found as a result; and the rest of the speakers will be telling us about models of surveillance and things to do with the actions that are sometimes taken on the basis of that. So, thank you.

FDA Safety Surveillance for Licensed Biological Products, Including Intravenous Immune Globulins

DR. WISE: Well, I am very happy to be here this afternoon speaking with you all. It is important for us to be diplomatic; as people trickle in, don't fix them with stares that make them feel guilty. Just enjoy the fact that you are here from the outset.

I am going to be describing the safety

surveillance process, particularly with reference to intravenous immune globulins at FDA's Center for Biologics Evaluation and Research. I do want to express appreciation to all of my staff, the Therapeutics and Blood Safety Branch at FDA, which has assisted in the preparation of this presentation and, of course, that staff is the set of people who are doing the actual work.

CBER, Center for Biologics, monitors the safety of FDA licensed or regulated biological products. Many of you are probably aware that these include blood components and derivatives, allergenic extracts, human tissue products, human cellular products, vaccines, toxins and antitoxins and devices that involve biological components.

We regard our mission as comprehensive safety surveillance. The labeled indications for IGIV products differ. Not all of them have clinical trial evidence of efficacy and safety for all of the IGIV indications. FDA does not regulate the practice of medicine. Off-label use of products that are licensed is legal and can be

medically sound. Our safety surveillance encompasses all product use whether or not a particular indication in a particular patient's experience is labeled.

The data systems that we have are primarily passive. Many of you are probably familiar with the terminology of spontaneous reporting and voluntary passive surveillance. The principal database for IGIV and similar therapeutic products is AERS or MedWatch. AERS is the adverse event reporting system operated by the Center for Drugs at FDA but it also serves our biological products other than vaccines. It contains data from adverse event reports for blood, derivatives, components and biological products, again apart from vaccines. Our staff monitor and evaluate the consecutive reports, particularly the expedited so-called 15-day reports. These are adverse events that manufacturers judge to be serious and unlabeled which they have to give to us within 15 days. We also receive and monitor direct reports, reports from consumers, pharmacists, physicians and

anybody which have not gone through the manufacturer.

We have the VAERS program for vaccines that we run in cooperation with CDC. Manufacturers provide periodic submissions of monthly infectious disease reports and quarterly or annual reports to us for all of the reported adverse events and there is a database of lot distribution information that we can use as a denominator to give us the size of distributed lots when we want to make comparisons, as occasionally is helpful.

There are advantages and disadvantages in passive surveillance like this. Strengths include the open-ended character which allows hypothesis generation without restriction to a predefined set of anticipated risks. There is potential detection of completely new or very rare adverse events; timeliness; geographic diversity encompassing the entire U.S. and actually beyond; and the capability to monitor safety of production lots.

But there are also limitations and disadvantages. Many of the reports have a lot of

missing or inaccurate information. There is extensive and generally unknown extent of under-reporting. We don't ascertain all of the adverse events that occur. And, there is no simple multiplier that we can apply to inflate the numbers that we do receive as an estimate of numbers of cases that actually occur because more serious events are more likely to be reported. There are all kinds of variables with publicity, recency of a product's introduction to the market, and other forces that are going to influence the extent of under-reporting.

We don't have control patients. We are just looking at the numerators. It is usually not possible to infer clearly whether a given patient's experience was, in fact, due to the suspect product identified or due to some other factors. And, there is a much lower likelihood through passive surveillance that we would detect adverse events that have long latency intervals. People are more likely to suspect and report a relationship with a drug if the interval between the onset of the

adverse event and the exposure to the drug was short.

Our role and goals in safety surveillance--most additions to safety data, operationally defined as the package insert or the professional package insert for labeling--after licensure stem from spontaneous reports of suspected side effects. So, they are certainly very important to monitor. Our objectives are to detect new risks, that is, previously entirely recognized reactions including medication errors, and to identify new information about known risks, such as a greater rate or specificity or severity of an adverse event than had previously been appreciated.

There have been historical situations, issues, problems which are very infrequent and none has occurred in the last several years that I recall, but these have been of sufficient gravity that we feel that they compel continued very close surveillance of product safety. We don't have to go through all of these in detail but they extend

from as long ago as 1901 to as recently as 1996 when vials of albumin were mishandled and were contaminated after completion of quality control procedures and checks in the manufacturing process. So, the bottom line is that although, for the most part, we find nothing and the absence of recent disasters or problems is testimony to the very stringent quality control procedures that are in place to assure that every lot of every product is safe and effective, nonetheless, we feel that it is important to maintain close surveillance.

Let me give a few examples of previous projects within our group, and then I will touch on a few examples of projects that are in process. We discuss albumin and intravascular hemolysis; IGIV and acute renal failure, and you have seen some of this earlier; and anti-D IGIV and acute hemoglobinemia.

Albumin is a colloid product for volume replacement. Between 1994 and 1998 we learned of 10 patient experiences. Five of these patients had acute renal failure; one patient expired from

complications. Osmotic lysis due to erroneous dilution of 25 percent albumin with distilled water seemed to be the basic underlying mechanism. The factors that contributed to this medication error included a shortage at that time of 5 percent albumin so that the 25 percent product was in use; a reference book ambiguity on dilution instructions, and the effect of the erroneous dilution was amplified by the extent of blood volume being replaced in plasmapheresis. As risk management interventions, we issued a letter to The New England Journal of Medicine. There was an MMWR and other articles published, and I believe that that problem was then controlled through that information dissemination.

This slide is only slightly rearranged from the one you saw earlier so I don't think we need to spend a lot of time on it. I would point out that there were 26 foreign reports in addition to the 88 U.S. cases that were primarily analyzed. I believe that we felt that the time interval was between licensure in 1981 through 1998. That may

be slightly different from the previous speaker's slide. Thirteen of the patients expired but they had severe underlying conditions so we didn't feel that they had died specifically and only because of the sucrose-containing IGIV. Several mechanisms may account for the renal failure, including but not limited to osmotic nephrosis.

IGIV in acute renal failure recommendations for prevention were transmitted through an FDA "Dear Doctor" letter; the addition of a black box warning to the package insert, the labeling, and an MMWR article. The thrust of these recommendations, as outlined earlier, was that physicians should weigh the anticipated value of intravenous immune globulin against the renal risk and they should assure that the patient is hydrated before starting an infusion, especially for high risk patients in these groups. They should avoid exceeding the recommended dose, concentration, and infusion rate and they should monitor renal function before and during infusion.

Anti-D IGIV and acute hemoglobinemia is an

interesting experience. Anti-D IGIV is mainly employed for idiopathic or ITP. Fifteen cases of acute hemoglobinemia came to our attention from licensure in March, 1995, through April, 1999. Eleven patients had developed clinically significant anemia, required transfusion, suffered acute renal failure, required dialysis or expired. The mechanism of the hemoglobinemia remains unexplained but risk management interventions included recommendations to monitor for hemoglobinuria during the infusion, anemia, renal failure and other potential complications. The manufacturer Cangene issued a "Dear Doctor" letter and revised the package insert and FDA published a manuscript in Blood.

A few examples of current projects include concerns about thrombotic events with recombinant Factor VIIa; thrombotic events with IGIV products; and anti-thymocyte globulins and acute respiratory distress. Recombinant Factor VIIa is the activated form of recombinant Factor VII. The brand name is NovoSeven. It is licensed for the treatment of

bleeding episodes in hemophilia A or B patients with inhibitors to Factors VIII or IX. But it is increasingly being used off-label for non-hemophiliacs. Case reports to FDA are describing a variety of arterial and venous thromboses in 17 hemophiliacs thus far--actually, this is through the end of 2004--17 hemophiliacs and 151 non-hemophiliacs.

The major safety concern in published literature on this product is the thrombotic risk in patients without hemophilia. Recombinant Factor VIIa generates more thrombin in vitro with normal blood than with hemophiliac blood. The formation of an undesired thrombus is also likely to depend on vasculopathy that exposes tissue factor, but it seems plausible that recombinant Factor VIIa's safety could differ between hemophiliacs and normal patients. Because most of the case reports also have other possible causes for thrombosis, we feel that only controlled clinical trials of recombinant Factor VIIa for additional potential indications would be able to clarify its safety and efficacy in

a non-hemophiliac patient.

Thrombotic events with IGIV products have been featured in published case reports for several years since 1986. A causal association has been presumed but has often been difficult to prove. We are in the process of comparing case reports that do and don't describe thrombotic events during or after IGIV administration for about the last 6 years. We are looking for possible patterns in IGIV products, patient ages, indications for the IGIV use, infusion concentration, infusion rates, and reporting rates, and this analysis is in progress. I don't have results to report.

Finally, we are in the process of looking at antimicrobial anti-thymocyte globulins and acute respiratory distress. These are polyclonal antibodies directed against multiple T cell markers. They suppress cell-mediated immunity. They are licensed to treat rejection after renal transplantation, and one of these products is also licensed for aplastic anemia. Published case reports and adverse event reports to FDA describe

unexplained respiratory failure, including ARDS, after anti-thymocyte globulin therapy. Sepsis is a recognized cause for ARDS so we are excluding infectious patients. Analysis of other reports of respiratory failure or distress in AERS is in progress now in order to evaluate the nature of these adverse events and possible mechanisms.

I think this is all I wanted to present at this time. I would be happy to take specific questions, or else we could wait for the panel.

DR. SCOTT: I think because of the time we will wait for the panel.

DR. WISE: Sure.

DR. SCOTT: Thank you very much.

DR. WISE: You are very welcome.

Utilizing Public Health Surveillance to Monitor Adverse Outcomes of Blood Product Therapy

DR. SOUCIE: Good afternoon. I am Mike Soucie. I am an epidemiologist at the Centers for Disease Control. I am going to try and go through these slides quickly because we are going to try and make up for some lost time earlier this

morning. Dr. Scott has kindly asked me to come and describe to you some features and some of the things that we have learned through our active surveillance system at CDC to monitor adverse outcomes of blood product therapy for patients with bleeding disorders.

I am in the Division of Hereditary Blood Disorders at CDC, and our mission, as mandated by Congress, is to reduce or prevent the complications of hemophilia and other bleeding and clotting disorders and thalassemia as well.

I am going to focus primarily on hemophilia because most of the information I have applies to that group. There are approximately 18,000 people in the United States with hemophilia and the treatment for a bleeding episode consists of infusions of biopharmaceutical products that are made primarily from blood. There is potential risk of infectious disease transmission, including hepatitis and HIV obviously. This was in large part the incentive for setting this up. Essentially, the hemophiliac population wanted a

surveillance system set up so that this would not happen again. CDC has established a public health surveillance system for product safety in this group.

Actually, I am going to skip over this slide because I think most of you know the difference between surveillance and research.

So, I will just move along and talk about, first of all, the priorities for this prevention program. These priorities were set by the bleeding disorders community, not by CDC. They, first of all, wanted blood product safety. They wanted information to be learned in surveillance of chronic joint disease that results from the repeated bleeds into joints. They wanted information collected about the specific problems of women with bleeding disorders, also talking about von Willebrand's disease in this case as well as female carriers of hemophilia; finally, detection of hereditary abnormalities associated with both bleeding and clotting disorders.

We run this prevention program through a

cooperative agreement through a system of hemophilia treatment centers, which are really clinics operated in educational institutions throughout the Unite States and its territories, who participate in blood safety monitoring and surveillance efforts. They collaborate with us and lay organizations to deliver consistent prevention messages to patients and to maintain a prevention evaluation network to assess the efficacy of these prevention efforts. In other words, part of our surveillance is to identify potential prevention steps. The other part of the surveillance is to monitor and to assess whether or not these interventions are having the desired effect.

The blood drops here show the distribution of the hemophilia treatment centers. We also have on in Puerto Rico and one in Guam. The others pretty much follow the distribution of the U.S. population.

We call this surveillance system the Universal Data Collection System, or UDC for short. The purpose is to monitor blood safety; to monitor

the extent and progression of joint disease, primarily in individuals with hemophilia and other bleeding disorders; and to identify issues for further study, and I will give you some quick examples of those as we move through.

The way that this is set up is through a national protocol that is approved by the CDC and local human investigational review boards of all 134 of those institutions, which is a full-time job in itself to just keep all that information up to date. We have standardized data collection tools that were designed from using input from experts, again focusing on the issues of our target priorities as identified by the community. We request a blood specimen from each person who enrolls in this project which is tested centrally for the known infectious disease agents, including hepatitis and HIV. And, we also store a portion of the blood specimen for future investigations. We investigate any new infections that occur from one year to the next for any link with product use.

There are three components to it from the

patient perspective to let them know what it is all about. It is voluntary. We have the data collection by HTC staff and a blood sample is drawn, as mentioned before.

Some of these details I am want to skip over in the interest of time, but the data forms development is really a key feature to this. You need to understand exactly what it is that you are setting out to look for, and you will get lots of ideas at the beginning and the hard part of it is narrowing it down to just the important things because, again, these projects are done on the basis of people who are not employed full-time to collect surveillance data. They are usually busy clinicians and you don't want them spending any more time on this than they have to.

The purpose of this slide was not necessarily the names, although you may know some of these names. The purpose is to show you that it is a multi-disciplinary group. It includes physicians, nurses, social workers and physical therapists who work in these clinics and take care

of the patients.

The implementation of this involves training and providing support materials. People need to know very clearly who is eligible for the surveillance. They need to know exactly the definitions for the data elements so that everyone across the country is collecting the same data so that when it comes to analysis you know exactly what you are analyzing. And, there are issues of training in terms of handling the specimens and shipping them according to federal regulations, and so on.

We do range of motion measurements on the population. You would think that doing range of motion measures is pretty much standard but we have found out otherwise when we decided to do this, and there are many different ways of doing it so we provide detailed information on exactly how it should be done so that we get consistent results.

The patient is educated about the project. We obtain informed consent, and they are assigned an identification code which is only linked to the

patient at the treatment center. We get the identification code and that is so that we can provide the results of the testing back to the center and they can link it back to the patient.

Again I will skip over some of the details here, but we have a couple of different forms depending on the kind of information that we are collecting. Clearly, some of the information, such as the type of bleeding disorder and the age diagnosed, never changes so we just collect that one time. Then we have an annual visit form that is focused on things that change and on the target key issues that we are trying to follow in the surveillance.

Because we started this out in 1998 a lot of the centers did not have computers. So, we started out with the lest common denominator, filling out paper forms and sending it to us. We would enter the data, generate error reports and fax those back and have them correct it. We are currently in the process of switching to an electronic clinical database that is going to be

used by all the centers and that automatically generates the data from the visit and sends us the data electronically, which is going to give us a lot of flexibility in terms of being able to make this surveillance project more efficient in the future. A little bit of an idea of where we have come since May of 1998, more than 16,000 unique individuals with bleeding disorders have been enrolled, and they are asked to participate in the project by giving a specimen and by having data collected each year when they come back for their comprehensive visit. So, we have had probably over 40,000 visits now and that means 40,000 blood specimens that we have in the freezer at CDC for any future blood safety investigations. Our overall national refusal rate, which we are very proud of, is under 10 percent, which is almost unheard of in projects like this given that patients have to stay longer to get their joints measured; they have to get stuck when they might not necessary otherwise get stuck. And, we take it as a measure of the acceptance and approval of this

project by the hemophilia population or bleeding disorder population.

To date, with our blood safety monitoring we have had no new infections with any of these viruses that were due to blood products among UDC participants. Also, as a prevention message we are encouraging all these patients to be immunized against hepatitis A, particularly those who are HCV positive, and we believe that this constant monitoring is providing reassurance to the bleeding disorder community of product safety. In addition, we are developing a serum bank for future use. I wanted to give you a couple of examples of what we have used that for, one with West Nile virus and another standard parvovirus B19.

All of you know there is evidence from the community for blood-borne transmission of West Nile virus. Although the products used by the hemophilia population are subject to viral inactivation that probably takes care of West Nile virus, it is not really known. So, we have been taking specimens from patients who were seen in

previous mosquito seasons and we have been testing them for West Nile virus. To date, we have no evidence that West Nile virus is being transmitted through blood products.

The other blood safety investigation that we have done with serum specimens concerns parvovirus B19. I have heard a little bit about that this morning from some of your discussions. All of you know this is pretty much an ubiquitous virus. It usually causes just a self-limited illness in children. However, Parvovirus B19 has been known to be transmitted through plasma-derived products. It is resistant to viral inactivation and to filtration because of its small size. So, this study was designed really to determine if children who use recombinant products, those being theoretically less susceptible to B19 contamination--whether they were at less risk for getting B19 infection. And, a secondary analysis because we had information on joint range of motion in these children, whether or not the range of motion limitations were different based on their

B19 status. Some of you probably know B19 is associated with arthritis in some cases which can be chronic arthritis, and it has been associated with chronic infection in rheumatoid arthritis.

In our results from this we had about 10 percent of our population--these are very young children, between the ages of 2-7. They were born after licensure of recombinant product. About 10 percent of them had not had any exposure to either blood or blood products that we used as a reference group. We can see that those exposed to recombinant product alone during their lifetime were no more likely to be B19 positive, whereas those who had some plasma-derived were about twice as likely, and those who had plasma-derived products alone were nearly 8 times more likely to be parvovirus B19 positive.

The question is, does that make any difference? This is just a childhood illness; most people get it--no big deal. Right? Well, we looked at joint range of motion limitations by age in these same patients and you can see that for

each age group the percent range of motion limitation was greater in every age group for children who were B19 positive compared to those who were B19 negative.

I wanted to describe one other study, if I might, using these data. We are interested in describing the range of motion limitations by age and hemophilia severity and to examine the associations between risk factors and why some kids were getting more limitations in their range of motion, more range of motion loss, than others. What were the risk factors involved? The reason I wanted to show you this example is to show you how we take this information and then translate that into preventive steps. The brief summary of the findings was that range of motion limitation patterns vary by severity and that they develop at a very early age. We found that the factors associated with range of motion limitations also vary by severity. One real key finding regardless of severity is that we found that overweight was a potentially modifiable risk factor for the range of

motion limitation. When you think about it, this is pretty much of a no-brainer. If you are overweight you are putting more stress on your joints and probably contributing to bleeding episodes.

However, we now have it in the data and the question is what is the magnitude of the problem. Do the people with hemophilia have the same problem that we have recognized in the country with overweight and obesity? We are able to use our same surveillance data and I will just point out one group--I am sorry, it is small for those of you in the back, but I will just point out one group, the 13-19 year-olds. As you know, there is no obese category, it is overweight depending on being 95 percent over the limit. But we found that 18.2 percent of patients with hemophilia and 17.2 percent of patients with von Willebrand's disease were overweight as opposed to 11.5 percent in the U.S. population so nearly twice the prevalence of overweight in our patients with bleeding disorders. This may have something to do with the fact that

they have experienced problems of trying to get out and do a lot of physical activity and perhaps became more sedentary and overweight. So, the problem is a big problem. It is an even bigger problem in this population. Not only are there more patients affected but it has implications for their long-term joint status.

What we have done with this information is we are working on developing prevention messages. We are reevaluating the current prevention messages in the light of these new findings. And, we are working with our partners to develop population-specific prevention messages for the bleeding disorders community. We can't just tell them to go out and play more basketball, more football or something like that obviously with hemophilia. So, they need to be specific for the population.

This shows our National Hemophilia Foundation is one of our lay organizations that we work very closely with. You can see a lot of those recommendations there are things that we promote

through our monitoring activities. You will note #4, regular physical exercise, and we are probably going to extend that to regular physical exercise and maintenance of proper weight.

I am going to skip this slide and just tell you that if you would like to know more about this project, we have routine surveillance reports and published articles. We have national and regional reports on the web site where we provide these data back. A really important part of any surveillance system is to get this information back not only to the people who need to know but also the people who are working out there to collect these data to make sure that they understand that we are using these data and it is not just going off out into a black hole.

This is our easy to remember, user-friendly web site address. It is actually much easier if you just go to cdc.gov. We have A-Z topics. If you look under hemophilia you can find our web site and all of our surveillance activities. Thank you very much.

Perspective Post-Marketing Surveillance of Octagam

DR. MILLER: Good afternoon. I would like to thank Dr. Scott and her colleagues very much for

inviting Octapharma and providing us with the opportunity to present our approach to adverse event surveillance. I am going to report on the 10-year active post-marketing surveillance of Octagam in Germany.

I would like to start, rather than as is normally at the end, by acknowledging my colleagues in Germany. This is their study. I am reporting on it because I live down the road. It is also because I have been with Octapharma for 13 years. As you probably recognize, this is not a local accent. Although I currently work as the medical director for Octapharma here, in the U.S., I have been with the company for 13 years so I have seen the study evolve and develop.

I am going to give you an overview of this study. I would like to tell you why we did it; how we did it; what we found out; and basically what lessons we have learned from it. Our rationale for

performing this post-marketing study was very much based upon the time at which Octagam was launched in Europe. At that time we had just been through the HIV crisis, the hepatitis C crisis and there was a lot of concern about blood products, and in particular their viral safety. There was also a lot of data that was published about the clinical tolerability of IGIV.

We launched the project in 1993 which was immediately around the time at which a number of hepatitis C transmissions were being reported with non-virus inactivated preparations, and people were not only concerned about the viral safety but also about the limited long-term usage. As so many speakers alluded to this morning, there were no head-to-head studies of IGIV preparations outside those performed by the same manufacturer. The tolerability data in the literature is extremely confusing. Depending on which studies you read, it is somewhere between 5 percent and 81 percent. And, there was no prospective requirement to do post-marketing surveillance in Europe.

We, therefore, felt as a company with a new IGIV facing this background of concerns in Europe, that it was up to us as a pharmaceutical

industry to drive the initiative for active post-marketing surveillance. We hoped by performing this study that we, at least internally, would be able to better understand the type of side effects, the type of adverse reactions that were occurring in routine clinical use with our product. As several of the speakers pointed out this morning, the clinical trials that have been performed with IGIV have mainly been on small homogeneous patient cohorts. If I may borrow or adapt an expression from Dr. Dash, they are mainly done on the "non-rogue" patient population. We eliminate all of those patients who have previously had adverse events in classical licensure clinical trials. But that doesn't answer the questions of clinicians who say what does it mean in real life. We also wanted to look at tolerability of our product over a long period.

So, how did we go about doing this? Well,

we designed a prospective, post-authorization, multicenter study. This has now been running for 10 years in 245 centers in Germany. We deliberately designed this as an open study. There are no exclusion criteria. Any patient who has received Octagam may be entered into the study. As part of the protocol, we aim to document the nature and intensity of adverse events. We designed the study in a way that would allow us by this data capture to perform a subgroup analysis to look at perhaps risk factors for adverse events such as age, sex, type of indication for which IGIV was being used, and really to address more clearly if use always correlated with adverse events such as total dose and the infusion rate.

By making this an open study--and Dr. Wise just alluded to this, we did include patients in the study who were getting the product for the so-called off-label indications. Although, it was not our intention to promote in any way these off-label indications, I think most of us in this room are aware that a large amount of IGIV is used

in precisely this type of circumstance and the fact that these are not licensed indications means that there is an absence of data in the vast majority of clinical use. So, we could observe these conditions and we could also see to a certain extent, internally at least, how much off-label use there was at least in Germany amongst the centers in which the study was performed. Although it was designed primarily as a tolerability study, we also collected data on viral safety and, to a certain extent although minimally, on clinical efficacy, particularly in ITP looking at rise in platelet counts.

Because this was a prospective study and because it was a long-term open-ended study, we have also been able to capture not only the immediate type of allergic reactions but also delayed reactions, and by following patients over a long period of time we can capture any events that may have occurred between infusions.

Very briefly, the way in which we performed this is by anonymous patient

identification system. For every patient who is infused with Octagam the treating clinician or nurse fills out a detailed 6-page case record form which records such things as the patient's disease, their age, their weight, their viral marker status, any concomitant medication or illness the patient may have, the lot number of the product being infused, the exact dose, the duration of infusion and then, of course, whether side effects have occurred. If an adverse event occurs, then there are subsequent pages to fill out recording the nature and severity of the ADR. The data from these case record forms is entered into a central database. This is managed internally by Octapharma, and we do perform routine checks of the database to ensure both its plausibility and completeness.

I am afraid you don't have a copy of this slide in your handouts. I added it over lunch in response to a question that came up this morning. What exactly do we mean by adverse events? How are companies actually classifying these? I can't

comment for all studies but I can tell you how we did it in this study. We used the standard MedDRA classification so for adverse events that occurred within 13 minutes of the start of the infusion a mild adverse event was classified as no treatment being required other than non-prescription drugs; moderate, the infusion was slowed or temporarily stopped; severe adverse events were classified as those in which the infusion had to be stopped and the adverse event required follow-up treatment. The late adverse event classification--mild were those exactly the same as in the previous infusion type event. Moderate, again, required the use of prescription drugs, and severe required either hospitalization, doctor's visits or prolonged hospitalization.

This study has just celebrated its 10-year anniversary but it is still ongoing so this is an interim analysis of the data from the study's commencement in February, 1995 through to the end of February, 2005. To date, we have recruited more than 6,200 patients who collectively have received

over 90,000 infusions. Total adverse events in this 10-year period have occurred in 4.4 percent of patients or 0.36 percent of infusions.

In common with a lot of the information reported this morning, the most frequent adverse events reported in the framework of this study have been chills, fevers and rigors. We have seen no viral seroconversions. And, the vast majority of adverse events, of those 0.36 percent of adverse events, have been reported either as mild or moderate.

As previously mentioned, this is an open study so we have patients in there who have been treated for primary immune deficiency, for secondary immune deficiency, for HIV, for a huge range of autoimmune diseases which I will mention in the upcoming slides, for ITP and a variety of conditions that have been classified as "others." You will see that for the secondary immune deficiency group we split out the patients with HIV and those with non-HIV because I think we are all aware that most patients with HIV tend to have a

very low level of reaction.

Within these patients there were no exclusion criteria. There were no age criteria. We have premature neonates in this study and we have patients being treated, as was mentioned by another speaker this morning, for Alzheimer's who are in their late 90s. We have patients on very low dose infusion and patients on high dose infusion; on slow infusions and fast infusions. This data has allowed us to subset out the rate of reactions but in no patient group have adverse events exceeded 1 percent.

While not wishing to promote the off-label use, I would just like to list very briefly--and you have it in your notes--the type of autoimmune diseases that have been included in the framework of this study. The "other" indications were asthma, chronic fatigue syndrome, inflammation and infection, nephritis, transplantation and actually renal failure. As you can see, we have a lot of very sick patients in this study.

Coming away from the off-label use now and

back into the primary focus of primary immune deficiency, we have been able to go one step further than most of the published clinical studies which have just looked at total adverse events in primary immune deficiency and actually been able to subset them out. This, of course, has been possible because of the long-term nature and high numbers of patients in this study. As you can see very clearly from the data here, the vast majority of adverse events in primary immune deficiency occur in patients with CVID. We have had 3 reports in patients with total agammaglobulinemia. Interestingly, even in severe combined immunodeficiency, even in IgA deficiency where we know 20-30 percent of patients had anti-IgA antibodies of an IgE type, we did not see any adverse events.

Over the course of time we have been able to look at the frequency of adverse events. This is in all infusions now; we have moved back out of the PID group. I have listed all of the adverse events that have been seen in the framework of the

10-year study. As previously reported in the total slide, the most common of these was fever, occurring with a frequency of 0.063 percent. The next most frequent adverse reaction seen was headache and rigors but, again, with a very low infusion frequency.

More than 90 percent of the 0.36 percent of adverse events were of mild to moderate intensity; 4.8 were classified as severe. If we get a severe adverse event reported to us we will go back and do a causality assessment. Two life-threatening events that were reported to us both resolved without sequelae. We haven't seen any of the black box warning type of adverse events within the framework of this study.

Analysis of the database has allowed us to look at things such as the mean age of patients, which is round about 50 years of age which I believe ties in with the data that we saw previously today. We have also been able to look at subsequent infusions and patients who reacted once and--as again has been reported this

morning--went on to receive subsequent infusions without adverse reactions. Probably the most surprising observation from this study was that, unlike every other piece of literature we have seen reported, we found no correlation between total dose and adverse events nor between rate of infusion and adverse events.

What we have noted, however, is that different types of adverse events tend to be linked to different types of pathologies. Typically, we have seen rigors and fevers in primary and secondary immune deficient group, and we have seen the headaches in patients with autoimmune conditions, typically the neuro. patient group, and in those with ITP.

I believe that the validity of this study has been supported. If we look at the adverse event rate reported in our pharmacovigilance study over this 10-year period we have seen 328 adverse events. Passive reporting either through spontaneous reporting to our clinical drug safety unit, reports to worldwide authorities or

spontaneous reports that have appeared in the medical literature over that 10-year period have been very much less than those that we have seen in the pharmacovigilance study.

Our conclusion from this study over the 10-year period is that we have been able to demonstrate the tolerability of the product in a wide variety of clinical indications and a very diverse patient group. We believe that with each passing year and each analysis of the database we begin to gain a deeper insight into the tolerability issues that perhaps warrant further study, and the causality of ADRs, at least within our product.

I have already mentioned the legitimacy. In the same post-marketing period that this study is being performed, we know that we have sold more than 26 million grams, which equates to 2 million patient infusions and spontaneous reports have been very low. But by doing prospective active post-marketing surveillance we have perhaps been able to give a more meaningful figure the true

tolerability of the product.

Now, having said all of that, there are some logistical issues that have to be considered. In order to do a long-term study of this nature, we have found that a way in which we can obtain data is by paying the physicians to fill out these 6 pages of case record forms. Physicians are paid approximately $90 per infusion per day. With more than 90,000 infusions to date, costs in physician payments alone for Octapharma have been over $8 million. That excludes the time of the company for the data entry and constant data verification. It excludes the time taken for performing causality assessments.

Nevertheless, we believe that some of the lessons we have learned are valid. This database will be locked in April of this year and we do plan a major peer reviewed publication of the data. A smaller publication in the secondary immune deficiency patients was published last year in the European Journal of Hospital Pharmacy. But the study will continue at least in Germany.

The limitations of this study are very much similar to those reported by Dr. Wise in passive surveillance, namely, that we cannot say

that there is not missing or inaccurate data. We cannot say that under-reporting has not occurred. There is still an absence of controls, and causality assessments will always be difficult. Also, this is not a universal patient cohort; it only represents the patients and the physicians that have agreed to participate.

For the company and for yourselves, one of the major limitations of this data, because it is non-controlled and non-comparative, is that these results can only be interpreted in a descriptive manner. We cannot draw any competitive or comparative claims from this data. Certainly, one of the major limitations to performing studies of this type has been the data I showed you on a previous slide, namely, massive cost implications for the company.

Nevertheless, we believe that the study has provided both ourselves, clinicians and to a

certain degree patients and the regulatory authorities with data at least on the tolerability of one IGIV preparation. It enables us as industry to be able to answer clinical questions that come up on a daily basis with more statistically valid answers. I believe the open nature of the study has allowed us to answer a lot of questions that the type of licensure studies will never be able to answer because of the small patient numbers. It allows us to address many of those criticisms that were raised by speakers this morning of the homogeneity of licensure studies.

I suppose my final comment is to say that this was our approach. We took it once in one country. I am not beginning to suggest at all that this is an appropriate way to do adverse event surveillance. There are huge costs involved. Marcia Boyle just alluded to the fact that we are at a time of acute shortage of product. The industry has been under a lot of financial pressure. I am sure many of you are aware of the consolidations that have been going on amongst the

plasma products industry mainly due to the lack of financial viability of many of the companies and one has to question whether studies such as this are the most appropriate way for companies to be spending their money.

We must also question really what we have learned from this. Although the data is very interesting, has it really contributed anything to patient safety? That is a question perhaps you should answer rather than myself. Thank you.

MS. ROBERTSON: Before I begin, my name is Joan Robertson. I was formerly with Bayer Corporation but since April 1, I am now with Talecris Biotherapeutics, which is the company that bought the plasma products division from Bayer. The other thing I want to tell you is don't bother trying to look at the slides that you have in your handout because I focused a little bit too much on the recall and not enough on the communications so I have made some edits to the slides so if you try

to follow along it won't work.

I don't know how many of you know it but Bayer had an incident where we had a product tampering that occurred. This tampering occurred with our 10 percent IGIV S/D treated product. I think you will see as we go through this that the kind of actions that we took here for this technical complaint would also work if you saw an adverse event report as well.

In January of 2002 we received some technical complaints about some white precipitate in the product, loose over-seals, that kind of thing. We actually recalled the lot in February of 2002. Then after we did the recall we got some more technical complaints, and in March we actually were able to confirm that the product had been tampered with. Actually, somebody tried to dilute the product 1:4 with saline, and we recalled another lot in March of 2004.

I think, as you can see, that for any kind of technical complaint or adverse event timely follow-up is critical. You really need to have a

robust process to evaluate and respond to current technical complaints and adverse events. In our tampering case we, of course, did a comprehensive investigation and because these complaints come from outside the company you have to maintain close contacts with your external partners such as your patients, your physicians and distributors. Accuracy and timeliness of the information from your distributors or your treaters is key in these cases.

In the tampering case what had happened was that one of our distributors was purchasing Bayer product from a third party that it was not authorized to purchase. The distributors are only supposed to purchase their product through Bayer and this one had gotten it from a third-party distributor and they didn't disclose that information in a timely manner because it did violate the contract that they had with Bayer. So, it took a while to figure out what was going on. It would have been better if the information had been given up front. It could have been discovered

even sooner. Again, contacts with the regulatory authorities and discussions with CBER is key. Also, I think it is very important to inform your key stakeholders as soon as possible, which is something that Bayer did which seemed to actually work out very well.

Of course, the next step in the process would be what we call a critical action committee, which is a group of senior management that was to make a decision whether or not to take field action and then initiate the discussions with CBER. Of course, once you decide you have a market withdrawal or a recall you perform your lot trace and then you do a customer notification. In this case, when we did the customer notifications we utilized the patient notification center and then we also sent out prepaid postcards with the recall letters so that they could send back the postcard to basically confirm that they had received the recall letter and that they were returning any product that they had in their possession. For those people that did not respond back with a

postcard, they were contacted by phone or sales associates went to visit them, with the goal in mind to have 100 percent verification.

Some challenges to consider with any technical complaint or adverse event would be if they come from outside the U.S. It is often difficult to get adequate information to allow a timely investigation when you have complaints coming in from outside the U.S. You need really good relationships with your local agents or affiliates and face-to-face contact can often speed up the investigation.

Then, you also have to have an understanding of cultural issues. Many times people don't want to give you information or they don't want to provide samples to you because they are afraid they will lose their reputation, or they will lose face, or whatever. So, sometimes you have to deal with those cultural issues as well.

In the case of the tampering recall, as soon as we knew what was going on we partnered with the IDF as soon as the recall seemed imminent to

ensure that the patient population had complete and updated information. We maintained contact with the IDF throughout the whole process. We even provided funding to the IDF so that they could do their own mailings and it allowed them to get information out to their constituents within 24 hours of the tampering event once we had confirmation.

We also communicated by personal calls to key contacts. We did press releases. We sent out "Dear Customer" letters. We sent blast faxes to all U.S. hospitals and pharmacies, and we even consulted with Bayer's IGIV physicians advisory board and we asked them how would be the best way to get this information out to the patients and they provided us some good feedback.

We also developed this product integrity flier that explained what to look for in the case of a tampering. We educated our customers to identify the products that may have been altered in any way so that it would facilitate discovery. These information fliers were distributed by the

sales reps and they were also placed on the web sites.

Of course, in this information age web sites are a very good source for getting out information, and all the information that we had, all the letters and the product fliers, were posted on Bayer's web sites. All the press release letters and product integrity fliers were posted on patient, professional and industry organization web sites as well.

Of course, you have to have corrective actions any time you have an adverse event or a technical complaint that results in something like this and it needs to be appropriate to whatever cause was identified for the recall. The corrective actions have to be initiated with a sense of urgency. In this case the most expeditious thing would have been to find the person that did this and make sure he couldn't do it again. However, once we identified the third-party distributor CBER asked us to stop investigation and the investigation was turned over

to the Office of Criminal Investigation. We assume they caught the person but I don't personally know that.

But in this tampering case what we wanted to do was to do something to make it more difficult to tamper with the product. So, we put tamper-evident tape on the cartons, which was the fastest thing for us to implement. Since we were going to have some product out there with the tape on it and some without, we wanted to make sure that we educated all of our distributors what to look for and not to be too surprised if they saw some with and some without for a period of time. We also wanted to get a better and more efficient tamper-evident packaging feature so we developed the shrink-banding for the product and we phased in the implementation of that beginning in 2003 for all the liquid products.

We also put all of our distributors through a quality program, and if they refused to do the quality program they were dropped as a distributor for Bayer. So, we went from something

like 120-some distributors down to 20 because they had to pass this quality assessment that was done.

Also, in the case of the tampering we did do an audit of the distributor that was involved, the common distributor for all of these technical complaints we got. They were audited and actually at that point it wasn't determined that they had used a third party.

The lesson that we learned from this is that anything is possible. I think most of us never thought that we would ever see tampering with a biological product but we did, and it did happen. So, never say "never."

The other thing that we learned was to always question where the answers don't match the evidence. Everything that we were seeing with this tampering recall pointed to a tampering but we could never really get down because the distributor was withholding some information. So, you know, just keep at it.

The other thing is that open communication works. We were complimented on how well this

information went out, how comprehensive it was, and I think it works to involve your patient community as well. Thank you very much.

DR. SCOTT: I would like to ask the speakers to come back to be grilled by the audience, and Dr. Goldsmith is going to lead the discussion.

Panel Discussion

DR. GOLDSMITH: I would like to add my thanks to Dr. Scott and other people at CBER and other consultants who helped put together this workshop to try and identify what the agenda might look like for evaluating immune globulins in the future.

We are supposed to talk about safety here. I think you all spoke and you are all experts about safety. I wonder if I could just ask a question and see if that leads somewhere. I heard a lot of things in the last few hours about increased efficacy potentially of immune globulin products when higher doses are used. It seemed to me that there is kind of an undercurrent of moving towards

using higher and higher doses of immune globulins in patients with primary immune deficiency. I also heard a little bit of undercurrent that maybe some adverse events at least are related to higher doses or perhaps faster infusions, that kind of thing. I was wondering if people would like to maybe try and tussle with that issue. How do you balance those? How do you balance the idea that you want to take a life-saving drug and use it in the best way and most of the drug and, yet, it is a two-edged sword like a lot of drugs are? How do you balance this against safety issues? And, what can you do to learn about safety issues as you go along? That is kind of a global question but I would throw that out to the panel as a start and see where that goes. Bob is at least smiling so maybe he has something to say.

DR. WISE: Well, I thought I might pull a fast one and point out that you haven't asked about the larger question. If we increase the cost of therapy for the individual patient what are we doing to accessibility to therapy for the patients

who are on the margin and are less able to afford it?

DR. GOLDSMITH: Right. This is the lack of efficacy as a safety issue basically. I mean, if you can't get the drug it can't be effective so, therefore, it is unsafe. Right? Does anybody from industry have any thoughts about the idea of growing utilization of these products? Would this really result in some kind of increase in safety problems?

DR. SCHIFF: Well, I would just point out that the range of dose that we are talking about for immune deficient patients is still far less than what we are using in autoimmune disease. The other thing that we have found--and, again, most of this is anecdotal--but the patients that are well treated and you don't allow them to build up infections in between actually have fewer infections.

I remember one of our first patients and when we went from 100 mg/kg to 400 mg/kg, and he had 100 mg/kg and he turned cyanotic and he just

looked awful and I thought he would die when we went to 400 mg/kg and he didn't have reactions. So, I don't think it is necessarily a 1:1 correlation. I think in some cases rate can be an issue. That is fairly individualized. But the dose doesn't necessarily correlate. I think well treated patients generally have fewer reactions, especially the types of reactions we are talking about. I mean, when you are talking about 2 g/kg for patients, especially the elderly patients, I think there are some real concerns but that is, by and large, not for the group we are talking about now.

DR. GOLDSMITH: Do you think there really is any way to prospectively look for this kind of information? We heard some information from Europe. It was a costly endeavor. That was the punch line, it seemed to me. But, on the other hand, it was a way to try and learn about events that are not captured during clinical trials. The current paradigm is that clinical trials are 40 or 50 subjects and that we don't necessarily capture

the adverse events that are going to occur in a larger patient group over a longer period of time. Do you want to say something, Dr. Stiehm?

DR. STIEHM: We have sort of an unwritten rule at UCLA that patients over 65 have to be admitted to the hospital for their first IGIV infusion, and no more than 500 mg/kg and it has to be given over about 8 hours. The one possible suggestion would be to target those particular individuals that are getting that large dose initially for the first time. One group that is particularly susceptible is that 10 percent of IGIV is used by the dermatologists, and they use it in great quantities and they use it continuously and they are usually older patients so that identifying a group of particularly high risk patients might be of interest.

DR. GOLDSMITH: How did you come up with the rule at UCLA? Was there a committee?

DR. STIEHM: Well, there is a pharmacy committee which has to approve the use of IGIV, and what it is being used for, and how much is being

used so that they often consult me about whether this is a true indication for it.

DR. GOLDSMITH: Dr. Ballow?

DR. BALLOW: First of all I would like to congratulate Octapharma. I think that was money well spent and I think we need more post-marketing surveillance because, obviously, the Phase III trials are all done with very carefully scripted patients and you may get a completely different profile after it is out on the market, particularly for open-label use. If we are able to share that information with clinicians I think they can have a better informed opinion about product variability, particularly with patient selection because it is clear to me after looking at the literature that underlying risk factors, patient selection and product selection is going to be a very important factor in avoiding some of these adverse events.

I want to raise one question, if I can, Jonathan. Does anyone have a feeling for the difference with regard to either efficacy or adverse events in treating autoimmune patients with

102 g/kg given in a short period of time, in other words 48 hours, versus 400 mg/kg given over 5 days, as I believe they probably do more in Europe than in the United States? Is there any data on that as far as efficacy and tolerability?

DR. GOLDSMITH: Just to clarify, it might be just for ITP where there are published dosing regimens given over several days versus over a very few days but the same total grams of immune globulin are administered. That is what you are asking about.

DR. BALLOW: Right.

DR. GOLDSMITH: Right, just to clarify. Dr. Gelfand has a comment.

DR. GELFAND: I think [not at microphone; inaudible]... those are the two efficacy aspects. I am not sure that there are published data on adverse events [inaudible].

DR. GOLDSMITH: Let me hear from Octapharma.

DR. MILLER: I would like to thank you very much for your kind comments. We agree that

for us the money has been well spent. I was just very cautious in a roomful of very esteemed colleagues not to say that this is the only way to do it. And, I do believe it has answered some questions.

You are also absolutely correct in saying that the trend in Europe has been to move to giving these 2 g/kg doses over 1-2 days rather than the traditional 4-5 days as has been practiced here, in the U.S. Largely, that practice has come about because of the development of new tolerable products. I would say that when we published interim analysis data the first time of this study, it led many clinicians to feel more confident about giving these doses faster in autoimmune disease because of the fact that we weren't seeing a dose of infusion rates correlation and we weren't seeing the severe side effects. I am aware of the two studies that you mentioned, Dr. Gelfand, also one in toxic epidermal necrolysis where by giving faster you got much more rapid epithelialization by giving it in 1-2 days rather than in 4-5.

I believe, speaking to immunologists and colleagues around the world, there is at least a clinical belief that in autoimmune disease where

you need to modulate the immune system it makes sense to challenge it, and challenge it hard, and that perhaps giving it in very low doses may even in some patients be worse than not giving IGIV at all because of the propensity for anamnestic response.

PARTICIPANT: I have a little operational question. If you are going to do active surveillance, to what extent are you prepared to look at all the various preparations as generic in their reactions vis-a-vis product specific in their reactions? That has a great deal to do with how much surveillance you are going to have to do to get useful data.

DR. GOLDSMITH: I think the products are seen as independent products, that they are unique products. They have unique aspects of manufacture, and so on, and so they are basically assessed by the FDA on a case-by-case basis.

PARTICIPANT: They are in that sense but much of the data that has been put up here shows basically the same generic reactions from product, to product, to product. The patients seem to react to them perhaps with a different frequency but the same things are seen again and again. So, there is

some level of generic surveillance. I realize there is a disjunction between the regulatory aspects that you have to deal with and the surveillance aspects but that needs to be thought about when trying to decide what is the appropriate way to get value from the surveillance data.

DR. GOLDSMITH: I think the human body has basically a limited set of responses and if you want to characterize those as generic responses, then I guess they are generic but that is not really what they are. There is a unique data set for each product and if we look at what we get for our submissions they look different. If you look at the package inserts the adverse event rates are different. So, I think it continues along the same line. We only have certain kinds of responses that

we can make as humans. I think that may be what you are seeing. Dr. Stiehm?

DR. STIEHM: I would agree that if you are trying to get an anti-inflammatory action from high dose IGIV, then giving it all at once in a large dose might be useful. However, if you are trying to block an abnormal antibody, such as in ITP, subcutaneous might work just as well. In fact, many years ago we had some HIV patients that had thrombocytopenia and we gave them intramuscular RhoGAM subcutaneously and it worked just as well. And, there is a recent report, which I confess I haven't read, on using the IV form subcutaneously in the successful treatment of ITP. So, my suggestion is that if you are just trying to suppress antibody function, the subcutaneous route in perhaps a lower dose might be sufficient. Dr. Golding?

DR. GOLDING: I wanted to see if I could clear up something. I heard during the course of the day various adverse event rates to infusions of IGIV, and the general impression was that with the

recent products there was a much reduced adverse event rate and for the most part it was less than 1 percent per infusion. Then what struck me in Dr. Miller's talk is that she had a similar low adverse event rate except when she looked at particular diseases. Unless I misread the slide, when you had the CVID up there you had 20 percent which, to my mind, was similar to what we have seen with older preparations.

So, my first question is, is CVID an agamma unique population? Do they have higher adverse event rates to these products than other people? Did I misread your slide? DR. MILLER: I must apologize. In the interest of trying to make up time I did go through the data rather quickly. In the primary immune deficiency group of patients the overall incidence of adverse events was 0.6 percent of infusions. The 23 cases, I believe, in CVID were cases out of the total number of infusions but the incidence remained low as a percentage. So, those were actual adverse reaction numbers rather than a percentage. I can refer back

to that particular slide. In the CVID patients we had 71 patients, 1,700 infusions and 15 patients reacted to a total of 26 infusions. So, it wasn't a percentage.

But I think it was the first time that I have seen in any study the correlation between different types of primary immune deficiency diseases and the propensity to react. I think most people had felt until then that we were more likely to see reactions in the severe combine immune deficiency group who are rarely studied because the numbers are so low. However, again, our numbers are low. We have only had 5 but they have been infused on multiple occasions and we have never seen adverse reactions. We are still learning. With each interim analysis we are able to bring more meaningful data to the table.

DR. GOLDSMITH: Was your questionnaire an open-ended questionnaire?

DR. MILLER: Absolutely, yes, it was.

DR. GOLDSMITH: Because I notice the types of reactions seemed to me ones that I was familiar

with, anyway. I didn't see anything that I had never seen before as a reaction.

DR. MILLER: And I think we go back to the way in which you answered the question before, that does appear to be a generic patient type of reaction. I think the difference that is probably related is the frequency.

DR. GOLDSMITH: Thanks. Please?

DR. SOUCIE: I am not sure whether the question has been asked yet but it is the one about whether there is a place for active surveillance in all this. I have to admit that I didn't know a whole lot about this. I have learned a lot as far as these clinical issues, and I am a little bit confused about some things because I have heard, you know, conflicting stories about this and the other. But I guess in terms of just trying to frame this as to how it could be done, it is really going to depend a lot upon how this population is treated. In other words, are these patients treated in perhaps a few localized places, or are there places that see a lot of them? Because there

really are practical issues in terms of setting these up. As Judi mentioned, she had to employ physicians and we would sort of call that a sentinel surveillance system. She has a number of individuals who agreed to collect this information for her and that may be the way that this has to be set up. In our hemophilia community about 70 percent of the hemophilia population receive care at these centers so we can set them up. That has to be a consideration to any notions you might have for setting up an active surveillance system.

Beyond that, then it gets to issues. The things that I have sort of tried to simplify in my mind here--there seem to be two issues, one having to do with efficacy. As Dr. Scott mentioned, perhaps the products themselves are losing some of the antibodies because of the fact that people are not experienced in the diseases; they are just being vaccinated. So, perhaps the sample bank that she suggested would be useful in that regard; the monitoring of the number of infections that patients are getting, regardless of the dose and so

on. I heard that there are ways of monitoring progression of the chronic diseases. This would be something where you would want to monitor trends over time, which surveillance is really the best at, to see if these things are changing over time.

Then, with regard to the adverse events, I heard about a couple of the serious ones, aseptic meningitis, the cardiovascular and then the ones that are worth a bottle of wine, the ones that occur very frequently but we are not sure why those occur, those kinds of things could also be collected in kind of an active surveillance.

Again, the idea is not necessarily to answer the really tough questions you have about, you know, does it matter how much I give or how fast I give it but really some of the bigger questions, the questions over time that I have heard being brought up. So, those are just sort of my comments about active surveillance.

DR. GOLDSMITH: Dr. Stiehm?

DR. STIEHM: One possible mechanism of looking at adverse reactions is to use the local

blood banks. In many hospitals the blood banks really control the IGIV and dole it out. Furthermore, they often track transfusion reactions very closely, and they are responsible people and they have nurses that do the follow-up on an adverse reaction, and these are the patients that are most likely to get the severe reactions, the hospitalized older patients that are getting large doses of IGIV. So, one possible way would be using the blood bank personnel.

DR. MILLER: In principle I completely agree with what you have said and it is a good idea. I think though that for a lot of the clinicians in this room, and certainly having come from clinical practice myself, there is a large tendency to under-report, particularly the mild and moderate adverse reactions with IGIV, almost because they are expected reactions. We heard many times today that patients are routinely premedicated and that will interfere also to a certain extent with adverse reaction reporting.

I would like to point out just for those

of you who are interested, and it is a point I omitted during my presentation, the German pharmacovigilance study was undertaken in non-premedicated patients. And we did have to literally pay nurses and to educate each one of them that every adverse reaction counted and should be reported. I think the more I hear about it, since I have been talking to a lot of nursing staff both in the hospital and in the community in the United States, they frequently don't even make a note in any patient records if a patient gets flushes or headaches because they practically expect it, or they take measures such as pre-hydration or premedication to avoid it. So, I think if you are going to look at a blood bank method of surveillance there is going to have to be a huge level of education amongst the clinical staff before resorting to that approach.

DR. SCHIFF: You know, there are differences between Europe and the U.S., and there are differences between certain diseases. In Europe even with immune deficiency and the

autoimmune diseases there tend to be more patients treated within centers. With hemophilia, you are absolutely right, the majority of the patients are treated in a relatively few number of centers. This is a "do your own thing" country and we have been talking about trying to do post-marketing surveillance but I would estimate something like 5 percent of the immune deficient patients are treated in the major centers of the U.S. If you figure over 50,000 patients and figure out if we added up all of the major centers, you know, it is probably less than 5 percent. With the neurology diseases I think it is even worse. In talking to the neurologists, most of the patients that are not complicated are treated by community physicians.

So, I am not saying it is impossible but I think it may need a different paradigm to try to be able to capture these. I mean, I have gone so far as thinking that perhaps the only way to do it is that you have to be able to fill out a form in order to be able to get gamma globulin. I don't know who could mandate that but that may be the

only way to do the surveillance because unless it is mandated I don't think it is going to happen.

The problem with looking at hospitals is that you are looking at a very select group of patients. Yes, I think the hospital blood banks and pharmacies are relatively good. Again, if you require somebody to fill out a form, if it is totally passive it is not going to happen. But still you are going to wind up looking at a very select group of the sickest patients.

PARTICIPANT: I would like to support that because in the U.K. we ran a very comprehensive surveillance on Factor VIII and Factor IX with very high coverage of the total amount of product that was being used at the time. We tried to do the same with IVIG--or IGIV as you call it here, and there is another difference across the Atlantic--and we gave up because it was impossible to get anywhere close to assurance that we were going to capture the right group of patients. I think it is because the patients with hemophilia are treated largely in very confined centers. Even

those on home therapy have a very good, close relationship. You are dealing with IVIG with a heterogeneous set of diagnoses, a heterogeneous type of consultant looking after those patients, and it is very difficult to know precisely which patients are being used and how to actually contact them even in the main hospitals where this is going on. So, unfortunately, we gave up.

A positive side though from the U.K. is, and it has been mentioned a couple of times today already, the surveys that are being done by Nicki Brennan and her nursing team across the U.K. have actually produced some very good data. The rationale for them doing the work was to try to persuade themselves that home therapy with IGIV was a good thing and was not going to cause problems for patients, and I think they have been successful in persuading themselves that that is the case. Furthermore, that covers all products available in the U.K. at the time that the surveillance was going on, and the bottom line was that there is a very low incidence of adverse events and when you

look across the number of products that were being used in that surveillance, it is probably that there is not a lot of significant difference between the rates of AEs, at least when products are being used outside clinical trials.

PARTICIPANT: I wanted to ask the question--I certainly admire the post-market surveillance that Octapharma did. It was really remarkable. I think my question would be for the practitioners in the audience. As industry, you know, we have limited resources and that is a good example of one potential way to use your limited resources but it was a similar amount of money that it would take to do a licensure trial for a new formulation that was maybe more tolerable or a new virus reduction step that maybe added some safety to a product and at the end of the day we can't do both. So, the question to me would be what do practitioners find more valuable?

DR. GOLDSMITH: Any practitioners here? Dr. Gelfand?

DR. GELFAND: A very old practitioner I

guess. I mean, there are a couple of things that I think are important. First of all, those of us that work very closely with our infusionists and our nurses, all we have to do is listen to what they tell us. We find out very quickly about products and how they interact with patients. I was delighted to see with Octapharma that the CVID patients came up the highest. I would say that that is, for me, the most regular experience that I have for patients that have adverse events. The patients sent to me when they have a diagnosis of common variable immune deficiency--the reason I believe is that is an inappropriate use often of IVIG or Ig replacement because they don't need it most of the time. It is a grab-bag diagnosis. Most of the others on your list have a very defined diagnosis either on a genetic basis or otherwise. So, I think when we see patients who don't fit the defined diagnosis of CVID we should be cautious. In fact, Mark talked about those patients from Iowa that had the side effects for 3 patients with a diagnosis of CVID. In fact, I think one patient

was 79, another was 81--these are not patients that we would ordinarily put into our PID category. So, I think what we have heard today is that with PID the incidence of adverse events is very low, and whether it is 0.6 percent or 1 percent, it is very low and if we stay with the defined diagnosis it is probably even lower because the CVIDs may be diluted out.

I don't think we are going to easily product differentiate in PID. The incidence, fortunately, is so low it is going to be very tough. Where the differentiation comes up is as we increase the dose. We heard over and over again different side effects, severe and moderate, with those doses that are the 1-2 g/kg. If we increase in PID, if we aim for 1 g/kg, perhaps we will start differentiating there. But at the 400-600 mg/kg I don't think we are going to differentiate and I don't think we are going to utilize money wisely by trying to do a lot of surveillance because I don't think it is going to show up now with new products that are much more improved than they were in the

past.

DR. GOLDSMITH: I guess I would ask Miss Robertson is there any kind of communication strategy you could think of to try and build this up perhaps from the grassroots side? If we don't have an active surveillance program, is there a way to develop a more potent passive surveillance program, maybe built from patient organizations or that kind of thing?

MS. ROBERTSON: Certainly, in the case that we experienced partnership with the Immune Difficult Foundation and other patient advocate communities is a good thing. It gives them input into what is happening in their disease. I do think that input from them as far as what needs to be looked at, getting their feedback for what kind of events they are seeing is important.

DR. GOLDSMITH: I think we have reached the end--well, I guess one more comment.

DR. SCHIFF: Actually, I just had a question on a different topic. It is really about the FDA surveillance, Dr. Wise. That is, how are

the MedWatch reports handled on an ongoing basis? I mean, it seemed to me, for instance if you wanted to get Freedom of Information Act information out it is a very laborious process. Is there a computerized system so that you actually can have an active surveillance going on as these reports come in so that if you do get clusters of reports for a particular product or particular lot it can actually be picked up by your computers as opposed to being notified by industry?

DR. WISE: I regret at a personal level, but I don't speak for the government, the fact that the FYI process is laborious, time consuming, inefficient and costly. The MedWatch or AERS data--they are really kind of synonyms. The MedWatch is kind of the graphic user interface for the adverse event database. Those data are computerized and the actual reports are scanned so that they are accessible as images because often there is handwritten information that you can't get just from the computerized data. We have prompt access to those computerized data and we do monitor

them more or less closely. We are watching for a variety of things. We have various competing priorities and, you know, some signal could slip by unnoticed until some point later.

But we also have proactive data-mining techniques that we are developing, which we won't go into detail now, but there is a variety of ways that we use the computerized data which are promptly available to us within the government, and I am sorry that they are not as promptly available through the FYI channels.

There is also one other modality that might be worth mentioning that you would have quicker access to. Over the last year or so the Center for Drugs has begun to post the non-confidential components of the computerized data from the AERS system and MedWatch reports on a web site where those data are downloadable. Now, there is a delay of probably some months. It may be only the previous quarter that is posted, but those data would also be accessible for independent analysis without going through the FYI process.

DR. GOLDSMITH: I think we will call an end to this session. Thanks to the panelists and speakers. It was a very interesting session. I

will give the podium back to Dr. Scott, or should I introduce the next person? Dr. Golding is going to speak next. This is the session on IGIV licensure for treatment of primary immune deficiency.

DR. SCOTT: I think we can have a break actually.

DR. GOLDSMITH: A break has been announced, a brief one.

[Brief recess]

DR. SCOTT: In the interest of time I think we will get started. This next session concerns licensure, paths to licensure and something that is relevant to that at the end, the Critical Path concepts and potential application of the Critical Path. So, first I would like to introduce my boss. He is the best boss I ever had, Basil Golding, who is also the Division Director for the Division of Hematology. He was present and highly instrumental, along with Tom Moran and many

others, in designing a paradigm for IGIV licensure at a time when we had a shortage in 1998. So, we will begin with that. Thank you.

III. IGIV Licensure for Treatment of Primary Immune Deficiency

Immune Globulin Intravenous (Human)

DR. GOLDING: Thank you. After that introduction I think there is no way I can beat it, but I would like to thank you and Jonathan Goldsmith and Marcia Boyle for organizing this because it has been a very instructive and interesting workshop, and I think there are some action items that we can follow-up on which is very important.

What I am going to do is talk about the clinical trial design for primary immune deficiency which we set up several years ago. But as some background, as you know, plasma fractionation is a multi-step process and variations in the process can have far-reaching effects in safety and efficacy, and each product should be regarded as unique and immune globulins should not be treated

as a single generic biologic. We have heard several examples when people are talking about safety, for example the IgA levels, the big difference between IM and IV preparations which was probably due to aggregates, and we do see product to product differences which underscore both for safety and for efficacy that we should regard these as unique products and not as generic products.

In March of '99--this was during the time when we were aware of an acute product shortage--I think the first reports came in, in November or December of '98 and we were trying to respond to those to make sure that the studies that would be done would still be scientifically meaningful and would comply with FDA regulations but would be small enough to allow more studies to be done. What we first came up with was a prospective double-blind, randomized Phase III study which would incorporate both safety, pharmacokinetics and efficacy. This would allow for licensure of IGIV products and each new product would be compared to a previously licensed product and each arm would

have 80 patients.

You know, this evolved over several months with a lot of interaction between us and industry and the Immune Deficiency Foundation and they deserve a lot of credit for their interactions with us and for actually helping us come to certain decisions. The problems with this trial design, which we discussed at great length, was that there was a limited number of patients within the community of PID and these patients would not be enough to be recruited for many trials. There were also multiple new IGIV products that seemed to be in the pipeline and needed to be tested and, again, we were dealing with a shortage of IGIV.

So, we discussed various trial designs and at the BPAC of March 2000 this protocol was presented and the discussion was about possible trials that would reduce the sample size. Again, it would include PK studies. Some of the discussion at that time--we started talking about surrogate endpoints and there was actually a workshop where we discussed this, and the point was

made that you can use surrogate endpoints provided you show that the surrogate endpoints correlate with clinical outcome. Well, this is five or six years later and we still don't have any surrogate endpoints that meet that criterion of showing correlation of clinical outcome. So, there is no scientific basis or regulatory basis for not accepting surrogate endpoints. The point is that they have to be validated.

We decided to consider historical controls, and the justification for that was that IGIV products have been very successful in limiting infections in PID patients over about a 20-year period, and looking back at all the data, acute bacterial infections for patients per year, which were 4 or more without treatment, were reduced to less than 1 on treatment with immune globulin products.

So, what we came up with was a single-arm study. It would be a 12-month study and one of the reasons for having it over 12 months is that you would take into account any seasonal changes.

Obviously, certain infections are much more common at different times of the year. We would compare the data to historical controls for safety, pharmacokinetics and efficacy and, assuming 80 percent power and 99 percent confidence and one-sided testing, we could come up with ballpark numbers of about 50 patients for the study. So, the safety targets were based on previous trials.

In sharp contrast to what we are hearing today, we assumed at that time, in looking at all the trials that we could gather at that time, that the adverse event rate for IGIV per infusion was 20 percent. What we are hearing today is that it is less than 1 percent. So, I think this is one aspect of this trial design that we need to revisit and maybe change our actual numbers and recalculate them. But based on this number the target for the trial to exclude greater than 40 percent, 0.4 in other words at the 95 percent upper confidence limit, would be 40 percent or 0.4 doing a one-sided test, the sample size would be approximately 50 patients. We weren't prescribing the actual number

of patients in the trial. What we were saying to the manufacturers was if you use these kind of statistical guidelines you should come up with a patient number that you think would allow you to get approval of your product.

So, for efficacy we use an objective clinically meaningful endpoint. This goes back to the fact that we don't think we have surrogate markers. The primary endpoint would be acute serious bacterial infection. These would be predefined infections. We actually excluded acute or chronic sinusitis because of the difficulty of making a diagnosis.

Secondary endpoints were serum IgG levels and antibody treatment, hospitalizations, fevers and others. Again, the sample size should be sufficient to determine whether the infection rate for the new immune globulin intravenous product is at or below the belt line, which means less than 1 infection per year per patient.

So, the primary endpoint is acute serious bacterial infections. The infections per patient

would be less than 0.5 for approved IGIVs, and the data for this trial for the new product must exclude infections of 1 or less per patient per year.

The types of infection we were talking about, in nearly all cases what we would expect are positive bacterial cultures. So, we are talking about bacteremia and sepsis; bacterial meningitis; osteomyelitis or septic arthritis; bacterial pneumonia and visceral abscess. With these conditions it is usually possible to get cultures and to show that there are bacteria present in a very definitive way.

In terms of the pharmacokinetic data, we asked for at least 20 patients. There would be a washout period of 3 half-lives on the new product. Then, the various pharmacokinetic parameters that we measured would be the C-max, T-max, the area under the curve, the clearance and the half-life, and trough levels for at least 5 half-lives. The observed values should not be inferior to those concurrently or previously determined for approved

products.

The trial would be considered a Phase III pivotal trial sufficient for licensure. FDA at that time was willing to consider fast track because of the shortage of supply. As far as we know, at this time there is no apparent shortage. There were some calls that we got recently and we looked into this and, as far as we can tell, there is no shortage at this time but there may be some disruptions in distribution because of allocation and because of reimbursement changes.

The conclusions are that the number of patients per trial will be about 50, permitting concurrent trials of the new products. For appropriate approval, the new product would need to have acceptable safety, PK and efficacy profiles when compared to historical standards. And, we encourage sponsors to start collecting data during these trials to validate surrogate markers, for example, to look for titers of antibodies against specific pathogens. So, our hope was, and still is, that during these new trials data would be

collected which would allow us to determine whether titers against infectious agents could be used as correlates and could be validated as surrogates for infectious diseases and efficacy of these products.

So, what has happened since we proposed those clinical trial designs? If we now look at the rate of immune globulin intravenous licensure over the last few years, between 1996 and 2002 we didn't see any new licensure. We have seen two licenses in 2003, one licensed in 2004 and, for proprietary reasons, I am not allowed to talk about what is in the pipeline. But we do think that the changing of the trial design did make a difference to the ability of manufacturers to go out there and do these studies and get their products licensed in a relatively fast manner. What I think I have learned, at least from this workshop, is that we need to go back and look at our data set and the basis for some of our calculations and recalculate them and come up with more updated trial designs. Thank you.

DR. SCOTT: We have asked May Ann Lamb to

come and speak and give us the overall industry perspective on how this paradigm has worked from their point of view and perhaps what might be done to even improve it further.

Industry Perspective:

Current Clinical Paradigm for PID Indication

MS. LAMB: Good afternoon. I am Mary Ann Lamb. I am with Talecris Biotherapeutics, formerly Bayer. I am going to review some of the input from the industry on our perspective of the current paradigm that Dr. Golding just reviewed with you.

As was previously summarized, there was a change in the late '90s in terms of the clinical trial requirements or expectations for IGIV products and this created a challenge to the industry. There wasn't any published guidance and it required that we had multiple interactions with CBER to reach an agreement on trial design. Due to the limited patient population, it required extended periods for recruitment and enrollment of patients in these trials. It also prohibited parallel trials as multiple manufacturers were

trying to bring these products to market, and this was at a time when there was a shortage of IGIV.

The current paradigm was developed by CBER with significant input from the IDF and also with industry input to ensure that the current standards for safety and efficacy were met while facilitating studies to support licensure and enhance product supply. The trial design that Dr. Golding reviewed with you, the single-arm with historical controls, significantly reduced the number of patients that were needed to conduct these studies.

As he indicated, the current paradigm did facilitate the licensure of several new IGIV products. Three products have been licensed since the current paradigm was proposed. These included Gamunex, manufactured by Talecris, formerly Bayer, in August of 2003. This product was licensed with studies that were initiated prior to the availability of the current paradigm so this product was licensed under the gold standard of the double-blind, randomized Phase III study in comparison to a licensed product. Two other

products were licensed using the current paradigm, the Grifols product and the Octapharma product. There are other studies that have been completed or are in progress so other products will be coming to the market.

What has been the outcome of the studies using this paradigm? Multiple IGIV products manufactured by different processes have been demonstrated to be effective as replacement therapy for PID. This has been shown by the reduction of the incidence of serious infections, which was the primary endpoint, and other secondary endpoints, consequences of infection, quality of life type endpoints have also supported the efficacy of these products.

In terms of safety, the low incidence of serious adverse events for these products supports the relative safety and tolerability of these products and the current paradigm allows for the detection of serious safety concerns. There have been some products where development has been halted because of some safety concerns. However,

some of the adverse events that have been attributed to this class of products have not been seen in the clinical trials due to the low or very rare frequency of such events. These types of adverse events will only be seen with extensive post-marketing use, either through passive or active surveillance, and some may not be seen at all depending on the particular product.

Some of the adverse events that have been previously described may be product specific, related to molecular integrity, impurities, excipients or other formulation differences. Some adverse events are related to high dose medically necessary or unlabeled indications, or use in patients that are considered high risk.

What are some of the opportunities going forward based on some of the data that has been collected and used to license these products? The potential to extend the labeled indications for replacement therapy for secondary immune deficiencies based upon demonstrated efficacy in PID; the consideration of surrogate endpoints for

efficacy in future studies; revision of the paradigm to include a comparability approach that could be used for modified processes as manufacturers seek to improve their manufacturing process to improve yield, increase efficiency, etc.

What can be done to bring these products to market in lieu of doing clinical efficacy studies? Obviously, pharmacokinetics, safety both from the standpoint of safety as demonstrated in the manufacturing process and viral clearance steps, as well as clinical safety. Then, the opportunity to look at bioanalytical or non-clinical characterization to confirm the molecular integrity that the immune globulin maintains the appropriate functions, Fab and Fc; antibodies to panels of clinically relevant bacterial and viral antigens; comparability in terms of impurity profile, etc.

Opportunities to establish an appropriate balance between studies that are done pre-licensure, safety studies, and post-marketing surveillance studies, active studies to address the

spectrum of safety issues that have been discussed today while, at the same time, facilitating licensure. Due to the low frequency of some of the adverse events, the size of the trials that would have to be conducted pre-licensure would be very large and difficult to conduct.

Harmonization with international requirements, with regulatory bodies in other regions of the world and in particular Europe. And, the industry would appreciate issuance of draft guidance that would facilitate the discussion and help to establish some clear, appropriate and feasible path to approval for other indications in addition to PID. Thank you.

DR. SCOTT: I think we will progress from the current paradigm to the introduction of a paradigm or at least how subcutaneous Ig might be licensed. Paul Aebersold has worked on this for many years actually, and he is going to give us a summary of what we have requested and what can be done in this regard. As everybody knows, we don't have a licensed subcutaneous product yet but I

think it would be useful to mention to everybody what it may take to get one licensed. So thank you, Paul.

Regulatory Requirements for Subcutaneous Ig for PID

DR. AEBERSOLD: I am in the Clinical Review Branch and what I am going to present today is requirements--it may sound like a stringent word but you have to do something. There are, I guess, requirements even though you may not have heard them before. What I am going to present today is the thinking that we really put forward before any clinical trials were done and before we saw any clinical data. So, this is prospective kind of thinking that we did some years ago. I am always very hesitant to talk about data anyway because it seems like everything I know is confidential and I shouldn't say it.

Dr. Golding just went through all of this. I don't think I need to go through it again. That is for immune globulin intravenous. We heard a lot of talk this morning about what dosing levels are desirable or best for immune globulin intravenous.

I think we heard that there are some data about comparing different trough levels or different doses, but not a whole lot of data from

trials that would fit the paradigm of adequate and well-controlled where you could actually draw statistically valid conclusions about serious bacterial infection rates in two different groups. The 500 mg/dL is commonly accepted as a good trough level perhaps. We also heard a comment that this is in people who don't have any immune globulin to begin with, and if you have a baseline level of 300 or something, then you are not talking about 500 but some number added to that 300. But I will talk about 500 for agammaglobulinemia, recognizing that there are cases in which that doesn't apply.

I would also say, without giving any data, that it is our experience that some of these trials that we have looked at--that the subjects coming into these trials are not coming in at trough levels of 500. They have been on immune globulin intravenous and they are going into a trial with a new one and the general paradigm is that people

just take whatever dose they have been using, you know, in their personal practice worked out with their personal physician, and they just continue that dose but with a new product. So, the trough levels that we are seeing reported in these trials are not close to 500. They tend to be on average somewhat higher. As I said, this doesn't seem to be a bias of running a trial because if you were biased you would say, "well, we'll run the dose up for the trial because we don't want people to get any infections." No, they are just matching the previous dose. So, there doesn't seem to be a trial bias at all.

Now, for subcutaneous infusion of immune globulin we have to consider that there are losses in bioavailability due to the subcutaneous infusion compared with the intravenous infusion. This happens for a number of drugs. When I looked at some molecule drugs, there are some quite stunning losses. Actually, you see some reports of bioavailability less than 50 percent. But with this dosing formula, this is just the ratio of the

area under the curve that you get from subcutaneous to the area under the curve you get from immune globulin intravenous, and that is called the absolute bioavailability.

I give two examples, not about immune globulin but just to show that. Of course, this is a monoclonal antibody. In the package insert for Xolair the bioavailability is said to be 62 percent, subcutaneous bioavailability compared to IV. This is a fusion protein so it is not really immune globulin but it is a big molecule. It is injected subcutaneously. Enbrel is absorbed and its absolute bioavailability is 76 percent.

For these reasons, we were somewhat concerned about, first of all, how one would set up the dosing in a subcutaneous trial. You might not want to just match your previous immune globulin dose that you had been getting intravenously if you had been getting 200 or 400 a month--whatever you want to pick, say 400, should you then dose 100 per week but subcutaneous since apparently you won't get the same bioavailability?

That led us to wonder, you know, what should our dosing recommendation be for a subcutaneous trial, and the expectation would be

that the subcutaneous infusion is not going to have big peaks and troughs. It is going to be sort of rolling foothills, if you will, to the mountains, maybe even Kansas or something. And, the same monthly dose would have lower bioavailability. If you just split the monthly dose of IGIV in four you would have lower bioavailability. We weren't aware of any data from really controlled trials that would assess long-term outcome in terms of numbers of infections if you had lower bioavailability. So, if you switched and just automatically started having less bioavailability one might think that over a long course of time you would have more infections.

I need to credit this chart or figure here which, quite frankly, I just lifted out of a published paper, Andreas Moralis' paper. He is at the Swiss Red Cross, the OB central laboratory. It was a nice graph to illustrate some of the thinking

process that we went through.

I would also like to point out that just by the title here the question we were asking was should we match the trough when we are dosing subcutaneously? Should we match the area under the curve? What is missing from here, because we hadn't heard from Dr. Gelfand several years ago, was that maybe these peak levels are also very important. So, the peaks are not in this talk because I didn't have time to revise my slides since this morning.

Anyway, what we would be uncomfortable with is let's just say that this is some people who are getting their immune globulin intravenously and their troughs are around 500 and we were asking ourselves, "gee, if you switched over and you matched this trough level of 500, well gee, your area under the curve's going to be a lot less and clearly you have less bioavailable material." That doesn't sound like something you would want to do because, you know, people on immune globulin intravenous are only at the trough level for a

fraction of the month, whereas people maintained on a relatively flat weekly infusion subcutaneously might be not much above 500 ever. So, that seemed like, you know, maybe not the best concept.

So, here is the other concept. Of course, this also has a ramp up and we will come back to this slide later on. But matching the area under the curve would sort of say, okay, you are sort of flat here. If you are interjecting it intravenously you're higher part of the month; you are lower part of the month but on average it is the same bioavailable stuff. So, we thought, well, this might be a good way to run the clinical trial.

Why did we want to say that? That is because what kind of a clinical trial were we going to talk about? Are we going to talk about a head-to-head comparison of the subcutaneous infusion compared to an intravenous licensed product? You heard from Dr. Golding a lot of reasons and Dr. Lamb why those trials were probably hard to do. It is hard to find the number of patients and if we actually want to say anything

about the number of serious bacterial infections as a primary endpoint with statistically valid comparisons between the two groups, ruling out anything in the way of a reasonable delta, we would be talking about a larger trial than the 80 per arm that you just heard about. It could be quite something if you wanted to make a claim about the normal kinds of comparability with 20 percent delta.

The other totally different way is to say okay, well, we have a licensing standard for IGIV. Can we use something very similar for the subcutaneous trial? The point about the IGIV trial is this, what our current standard is, it really sets non-acceptable outcome. If your immune globulin is really messed up and you can't rule out one serious infection per year per subject and, you know, probably half the patients had an infection and, of course, if you had a really bad outcome, we are saying that is unacceptable; go back to the drawing board for some reason. So, it only sets an unacceptable outcome.

We have heard this from many, many speakers and I am going to say it again, comparison of efficacy data--and I should add or safety data,

and/or, from single-arm trials is not a scientifically rigorous, valid thing to do. Other speakers have said this. There are industry people here and I think the message should be that this remark should go back--not only mine but other speakers'--this remark should go back to all the marketing people of these companies because I know, and I have seen statements here and there, that marketing people think that they can make some claim that their product is better than another one because they had this result in a single-arm trial. No, that doesn't really work.

The concern about this unacceptable outcome is that there is a huge gap between where immune globulins really are in clinical practice and the historical controls. There is even a huge gap between where they are in clinical practice and what we are trying to rule out is an unacceptable outcome of one serious bacterial infection per

year. So, you could run a trial with suboptimal dosing--what do I mean by suboptimal dosing? Let's just call it low dosing for right now--and meet our standard. Yet, it could be suboptimal in the sense that if you had the luxury of a randomized trial with enough subjects for enough years to compare that dose or that dosing route of administration or process, or whatever you want to call it, to some other standard, like IGIV at trough levels of at least 500, you might beat our current paradigm, but if you had the perfect trial for a number of years, the gold standard trial, you would find out that it is suboptimal because patients would have more serious bacterial infections over the course of a decade. So, we have to recognize that running a single-arm trial doesn't really provide us much information. So, we have to make a guess about what to do.

Our guess about what to do was that we really didn't think we could support a trial in which subcutaneous administration would be targeted to a trough level of 500 mg/dL for exactly the

reason that maybe it would pass our standard because it is a very low hurdle, if you will, yet not be a good thing to do because people might ultimately have a lot more infections over the course of their lifetime than if they had a higher trough.

So, we came up with sort of a minimal expectation that if 500 mg/dL is a good trough for immune globulin intravenous the subcutaneous dose that we would entertain in a clinical trial would be that dose administered weekly by subcutaneous infusion that matched the area under the curve, gave the same area under the curve for the IGIV dose at least at an IGIV dose that gave a level of 500 mg/dL. But, again as I said earlier, people are coming into trials, it turns out, with a lot higher troughs on IGIV than 500. So, that was not particularly part of our thinking at the time. The conservative position is no matter what dose they come in with, if it is higher than that, still just to recommend matching the bioavailability.

So, in a graphical form, this comes back

to that same graph, and if this is people on IGIV with a trough of 500, we are saying, well, at a minimum subcutaneous dosing ought to give you the same area under the curve. Now, this is ignoring the fact that the peaks may be doing something very, very important. If they are, well, who knows when that will show up in the long run. But this was our thinking, that we should at least match the area under the curve and not have troughs that were down around 500 for subcutaneous administration. You know, the conservative way to think about it is, well, no matter what people were on before with IGIV, if they switched to subcutaneous infusion, you know, for their own medication background and choice of doses they ought to know and it might be a good way to start to dose the same area under the curve; give them a dose corrected to account for the losses of subcutaneous infusion, the lower bioavailability. Correct for lower bioavailability and that is the area under the curve.

That was our thinking, match the bioavailability of the previous IGIV dose; run our

belt line trial which provides just a minimum standard; and we would be left not really being able to make any comparative statements about whether it afforded equal protection or not but just feeling in some way that we had taken a conservative position to guard against lower bioavailability, lower doses of bioavailable material that could result in long-term worse outcomes for patients. That is it.

Results of the First Clinical Trial

DR. BERGER: I am Mel Berger, from Case Western Reserve University, and I want to thank the FDA and the IDF for organizing this conference and all of you for coming and staying through what looks like the bitter end.

I put up this first slide to give a bit of a historical perspective and a little anecdote that when Dr. Scott called me up and asked me if I would present the results of the first U.S. trial I said, "well, do you really want me to present again the results I presented to the workshop on IVIG that John Finlayson had 25 years ago?" Really, I had

done a trial of subcutaneous IM or immune serum globulin using the old 16 percent preparation before there was an IV preparation licensed in this country, back when I was a Fellow in Building 10--I must say, longer ago than I would like to admit.

The single patient that motivated me to try that was this patient whose management was very problematic. As Erwin said, if you ever had 2 cc of 16 percent immune globulin in your butt and didn't want it again, imagine what it would be like to take 50 cc a month, 10 cc a week or whatever the doses we were using at that time. We had this patient who was non-compliant, wouldn't come for her IM shots and then would present with serious infections. Then she announced that she was getting married and wanted to get pregnant. I had known about these small pumps being used for Desperal and we used that small syringe driver pump to give this patient the 16 percent IgG very slowly, and she was able to quite successfully carry her pregnancy. At the time of delivery her trough IgG level was 800 and the baby was also

around 800, actually slightly higher than the mother. The way we achieved that was that for part of the third trimester she was actually taking 20 cc of 16 percent immune globulin a day, in other words, 3.2 g a day. Actually, for the bulk of the third trimester she was taking 10 cc every day.

So, it is feasible to give immunoglobulin subcutaneously. One can get effective blood levels, and it is quite tolerable for the patients. This idea was adopted in Europe, especially in Sweden, for a variety of reasons but it had not been adopted very widely in the U.S. until this trial. I have to say that I was not involved in the design of this trial, and Paul Aebersold and I have not met until a few minutes again, and I was not involved in any of the discussions of the study design but we were a participating site and I did have quite a few patients. I think we had 5 or 6 patients enrolled in this trial, and ZLB has consented to allow me to share some of the data from the trial.

So, this was basically a Phase III

open-label trial, designed to meet the paradigm that has been explained in the last couple of talks. The objectives were efficacy, with the primary efficacy variable to be less than 1 serious infection per year; pharmacokinetics to equal the area under the curve that would have been achieved with IGIV; and tolerability and safety. All together, about 60 subject were involved.

The initial starting point or the initial guesstimate of how to achieve equal area under the curve was to use 120 percent of the previous IGIV dose and to actually calculate what area this resulted in and allow a more proper correction to get equal area under the curve in a PK sub-study. That would be followed by a standard 52-week efficacy phase.

The design included a PK sub-study which initially enrolled 24 patients, of which 7 dropped out and 17 completed both the PK pre-study and the 52-week efficacy phase. Another 41 patients were enrolled only in the efficacy phase and 7 of them dropped out so that 51 patients completed the

entire analysis.

Paul Aebersold and I did not discuss our presentations and did not discuss our choice of words, but it is interesting that we have both chosen the same word and the way I would put this is that we have a dilemma and I don't think we have the answer. We don't know whether the peak is more important. We don't know whether the trough is more important. We don't know whether the area is more important. In the studies that were talked about this morning in which higher doses were given one reports higher troughs, but those patients almost certainly had higher peaks as well and there has not been any independent manipulation of the peak versus the trough until a study like this.

So, basically in using the term bioavailability we have a dilemma in using a non-equilibrium measurement of the concentration in one compartment, namely the intravascular compartment, and we talked a little about where could you sample it and how could you sample it and it is not that easy, but basically we are sampling

one compartment to look at the bioavailability or concentration of a drug which seems at equilibrium to be distributed into two compartments but we are describing the measurement in one compartment as bioavailability. Again, I would say that I am not meaning to conflict, just that we don't know.

This was the study design that was adopted by ZLB in order to determine--I guess it was really Behring, then Aventis-Behring and now ZLB-Behring which is how the owner of this study was consolidated. So, first the patients were equilibrated on a standard dose of intravenous gamma globulin. Then they had a pharmacokinetic analysis for one month following the intravenous dose. Then they were given another intravenous dose and then they were started on weekly subcutaneous. Initially this was given as 120 percent of the intravenous dose. I must say that any argument over what is the preferred variable or how we should do this analysis aside, the single most important thing is to protect the patients, and I absolutely agree with the idea of using the

conservative assumption to protect the patients in the face of the unknown.

So, to start out with they used 120 percent of the IV dose. They continued the patient on subcutaneous treatment and then after 3 months on subcutaneous treatment at 120 percent they did another pharmacokinetic analysis. Then they calculated the necessary dosage adjustment to get the same area under the curve. They reassigned the patient dose and they continued the patient on that for another 12 months. The mean of the pharmacokinetic patients showed that the subcutaneous dose required to get the same area under the curve was 137 percent.

This is the data from one of our patients who was an XLA patient so we don't have this question of what was his baseline. On the standardized intravenous treatment he was on a little more than 400 mg/kg every 3 weeks. Here was his IV, the curve from which the area was calculate to make his final adjustment. You see the typical very sharp peak. The C-max here is 1,500, within a

few hours immediately upon concluding the IV infusion. It falls very rapidly as this redistributes into the second compartment I showed on the other slide. This is not on a log scale so you don't have the typical straight line but then it is catabolized with a half-life of around 20-some days.

Here you see the same patient on weekly infusions at a 20 percent higher dose of the 16 percent subcutaneous product. The mean is almost exactly the same. The trough here was around 560 and here it was 800-something, almost 900. This is the real data that was actually achieved for this patient. This would not have been quite enough, 20 percent extra. The patient actually would then have been given 30 percent extra to complete the study.

Once the PK subset was analyzed and this conversion factor of 1.37 was achieved, the patients were given individually standardized precise doses. They weren't given unit doses, as I have talked about in some meetings. So, the

patient was given an IV infusion and then started on subcutaneous. After a washout phase, they then entered a 12-month efficacy phase.

This was the European study of the same product. The European authority does publish guidelines. Their guidelines are that you have to get the equivalent trough. I am not going to discuss this at all but just say that all of the manipulation of the doses was not done in the European trial.

The efficacy endpoints in the North American trial were, as you have heard, serious bacterial infections per subject per year and all infections per subject per year. The results show that there were 0.4. Again, this rough guideline which is a minimally acceptable standard that Dr. Golding talked about of one infection per patient per year--we are doing much better than that now. The upper bound of the 99 percent confidence interval for that would be 0.14 which is still much less than the standard. The annual rate of all infections, which now includes all sorts of

sinusitis, viral infections and what-not, was 4.4. This was using 137 percent of the previous dose. Without going into much detail, I would just say that the results of the European study, which was only 6 months but annualized, using 100 percent of the dose were quite similar and I just put them up there to show that both studies gave very similar results.

The trough levels on this 137 percent dose increased by 255 mg/dL and the trough level that was maintained in this study was over 1,000. The mean dose was approximately 160 mg/kg/week but you see this tremendous range and, again, everybody in this study started with their previous Ig dose. So, you see this tremendous range, and the range selected for individual patients in conjunction with their individual doctors is much greater than the 37 percent plus/minus and I think there is a take-home message there. Again, for the European data the range was not quite as great.

So, the summary of efficacy for the North American study, 136 percent resulted in similar

rates of serious bacterial infections to what was achieved with 100 percent in the European study, and seemed to be as effective as the intravenous products although we wouldn't really make a rigorous comparison about it. It certainly met the standard.

Looking at safety--this 3001 is the North American study; 3002 is the European study--65 patients started out and 100 percent of these patients had some adverse effect. A lot of these were infusion reactions, local site reactions which I will show you in a minute. Only 13.8 percent of the patients had serious adverse effects. None of these was related to the product. There were no deaths. Five of the patients discontinued the drug due to adverse effects and 3 of these were due to injection site or study related AEs. The fourth one was not related to the injection site itself.

In the American study 92 percent of the patients complained of an injection site reaction sometime during the study. About half of the patients had a headache sometime during the study.

You can see a lower incidence of other adverse effects. Again, this is looking at the population of CVID and X-linked agammaglobulinemia and we know that in the CVID population there are lots of chronic complaints.

If we look at the adverse effects that were related to the study product itself, 92 percent of the patients reported injection site reactions; 32 percent reported headache; a lower percentage of nausea and fever.

This is a graph of the infusion reactions reported by women and by men over the course of the weekly subcutaneous infusions. I have no idea what the difference in reporting rates amongst the genders mean. There could be a biological difference or it could be a psychological difference. One important point is that as the study goes, as patients become experienced with subcutaneous they report less adverse reactions. It seems to me that some of this is actually less secondary inflammatory reactions at the sites and some of it is just getting used to the fact that

you are putting a volume of protein-containing solution in your skin and you are going to have a little local swelling.

Mostly the reactions were mild or moderate. There are pictures in the handout which will be on the web site so you can see these. Severe local reactions were very rare. The incidence clearly decreased during the study and only 3 patients withdrew because of these reactions and I think that is really the take-home message.

So, overall we had a good rate of serious bacterial infections, certainly much within the belt line. The annual rate of any kind of infection was similar. Certainly, the sponsors consider the injection site reactions safe and well tolerated and overall acceptable. So, thank you very much.

DR. SCOTT: We are rather low on time but I think we could take one or two questions for the presenters, if any.

PARTICIPANT: Mel, I was surprised that the incidence of headaches was that high. You

know, I thought that with the intravenous route patients were getting headaches because they are getting a bolus infusion and this is, you know, a more constant infusion. Your headaches were as high as 36 percent per patient basis or 45 percent per infusion.

DR. BERGER: Yes, the number of headaches that were attributed to the product was about two-thirds of the total number of headaches. My own impression, and the impression of patients who choose to go on subcutaneous, is that the headaches are much less severe than the kinds of things you are talking about after the large bolus. I suppose if the patient is sitting there with an infusion for several hours they may report a headache during that time. I am surprised it is as high as it is also.

PARTICIPANT: Were the patients preselected? Because a lot of times we put the patients on subcutaneous because they have headaches with the intravenous route. I don't know how the patients were selected for this study.

DR. BERGER: I don't know. I only know about the patients at our site.

PARTICIPANT: Because it is my impression

that the patients who consented to go on this study were ones that tended to have more problems from the intravenous route. I don't know if that is true or not.

DR. BERGER: It could be. I don't actually have data on that and I don't know if that data was actually collected.

DR. PIERCE: I just have a quick question. This is Dr. Pierce. If the quoted rate of serious bacterial infections per year was validated infections, and if that was the case, were there any patients who had an infection that was not counted as a serious bacterial infection because in order to be validated they had to have an imaging study? We have heard sometimes that some investigators are reluctant to do chest x-rays on children below a certain age with bacteria pneumonia. So, you could have patients who actually had a serious bacterial infection but it

doesn't get counted because of the way that the trial defines a validated infection. So, I just wondered if that came into play in either of these trials.

DR. BERGER: I can't really answer that question. I wasn't involved in designing this and I must say it was a couple of years ago. I am more familiar with the more recent things we have all these measurements we are taking in pneumonia, all the different parameters now that we look at to help understand the definition of pneumonia. I don't remember, for example, whether baseline chest x-rays were taken in this study as they have been in the other ones which have now gotten licensure.

Critical Path Initiative

DR. SCOTT: Yes, I think that is the kind of detail that is certainly interesting to know and probably another one of our reviewers could answer it for you at a later time. We will go on then to the last couple of presentations and then I will take the last five minutes to wrap up.

I am going to talk about the Critical Path

initiative and how that could be applied to immune globulins. First I just want to define the Critical Path. This is a new effort initiated by FDA. What is the Critical Path? Well, it is that time during which there is the translation from drug or biologic discovery to licensed products. So, that includes the preclinical and clinical development, the application and the approval.

So, why have a Critical Path initiative? I will tell you more about what it is, but the concept is to improve that Critical Path to make it faster, more streamlined and more efficient. There has been a decreased number overall of BLA applications in spite of a lot of research advances in understanding of both products and diseases overall for biologics. However, the probability for biologics and drug licensure once a Phase I study has begun has not increased since 1985, and there have been the observations that there have been a number of late failures in the course of product development, that is, when a Phase III pivotal trial has been performed. So, this results

in a great deal of expense for industry, effort for investigators and the subjects; a great deal of time wasted in both respects; and opportunity cost.

The tools of a Critical Path are defined as those things which can predict whether a product candidate will be safe and effective. That way, the sponsor can decide which candidates to move to successively more rigorous phases of testing. Also, tools may assess whether a product candidate is safe and effective once the potential product is moved into human testing. Critical Path tools may also facilitate manufacture of large amounts of product with a high product quality.

Examples of Critical Path tools would be animal models of human disease; biomarkers, that is, physiologic indicators that can be used to measure the progress of a disease or the effects of a treatment before other indications are apparent. It is a similar concept to surrogate markers or accelerated approval. It streamlines clinical trial designs, and I think that is something that we have approached today. I believe it was Dr.

Stiehm but also others have asked whether we can use antibody titer levels, trough levels of specific antibodies or other kinds of markers to streamline clinical trials. I believe the industry is also asking us whether they can use surrogate markers in the case of major manufacturing changes rather than going back and doing additional clinical trials for safety or efficacy.

Other aspects of clinical trial design that are important are providing guidance and guidelines for clinical trials for uses of immune globulins. And, quality assessment technologies--this would be in the realm of testing used to analyze product quality--are also things that we have spoken about today. These would include the specific antibody tests and also transferring from sort of old-fashioned tests, if you will, that are laborious as for example animal assays for antibody neutralization to more streamlined and less expensive but still informative assays.

And why is FDA involved? We can provide a

focus for Critical Path efforts because we have had a lot of experience in these products. Quite a bit of it may be unpublished and will never be published but we have a collective database or institutional memory for things that have been problematic. We can coordinate information and we can help initiate projects and collaborations to develop specific Critical Path tools.

We also are charged with evaluating for acceptance any such new tools, so new clinical trial design, new tests and so forth. And, we should also be in the position to provide guidance both for laboratory and clinically related efforts. We are also able to work with industry, patient groups, academia and government on all of the above. I think that this is not really just work for FDA but really it involves many groups and cooperation among us.

Finally, I put up Critical Path ideas for discussion, except we won't have a lot of time for discussion but I throw these out as potential Critical Path projects that could be done. One is

development of surrogate markers to predict infusion-related and other adverse events.

I think that the feeling, at least of many of us after today's presentations, and the clinicians can correct me if I am wrong, is that people do tend to continue their IGIV infusions on schedule in spite of the fact that they may have adverse reactions--headaches for a couple of days and so forth. But I would point out that it is possible to fail in a pivotal study based on these infusion-related adverse events because FDA does have a threshold cutoff for these so it becomes important to be able to at least predict or get an idea of whether your new formulation, for example, has this potential to have an increased number of adverse events beyond which it would be difficult to license it.

There is also the use of surrogate markers to support efficacy, especially in the setting of manufacturing changes but maybe also for the purposes of streamlining a clinical trial. We have not discussed that a lot internally but I think it

is something we all need to think about in the future.

We can streamline or help improve existing tests for lot release stability studies and for conformance lots. We could work on developing, with others obviously, paradigms for licensure of IGIV or Ig subcutaneous for non-primary immune deficiency indications. We all welcome input and identification of specific needs and ideas for Critical Path because I think there are still some problems to be solved in ways that we can improve getting product to patients and getting even better product to the patients.

Now our last speaker, also on the same topic, is Josh Penrod.

The Critical Path: The Plasma Industry Viewpoint

MR. PENROD: Good afternoon. I see the crowd has thinned but I am gratified to see that we still have a few interested people. It is always a challenge to clean up even though I am a lawyer and I can talk. I will try to be as brief as possible, although previous indications from my experiences

in past workshops are that if somebody warns the audience that they will be brief, in fact, it becomes quite long. So, I am telling you now this will be a very long and protracted talk.

My role here is to give you a high level policy overview. As you can tell, I don't really have a scientific background. I am a lawyer by training. Instead, I want to build a little bit on some of the policy topics that can be discussed in light of what Dr. Lamb and Dr. Golding have both stated. A lot of the stuff I am going to touch on--one of the areas of the Critical Path for example is industrialization and manufacture. I see Val Romberg in the back of the room. If I see his head explode, it is because a lawyer has just oversimplified an engineering concept.

But before I get into that, because I am a policy guy I want to clear up a potential misunderstanding that occurred earlier in the program, and Dr. Golding alluded to this as well, and that is the subject of an IGIV shortage. Industry folks do indicate that there has been a

tightening of IGIV supply in the U.S. Currently the demand exceeds other products. The supply must be stabilized in order to come into balance with the remainder of the product portfolios for most of the companies. This will create a better balance in terms of market demands and market dynamics.

Just as an overview, Medicare has put in place a new reimbursement policy--and this is not my field, I am sort of flying blind here--in 2005 which relies upon manufacturers reporting. Basically, what I am trying to say is that the reimbursement scheme has changed. It has moved to an ASP plus 6 percent away from an AWP. PPTA does share a concern that has been expressed regarding the payment rates established under Medicare Part B and the impact it might have on supply. But in response to the shortages that have been alluded to from the late 1990s, manufacturers have made enormous investment in staff, R&D, industrialization, and so on, and IGIV distribution is currently at an all-time high and is also serving more patients than it ever has before. It

has moved from 15,000 kg in 1998 to 27,000 kg in 2004.

Just to close out this little digression, certain PPTA member companies have put allocations in place to ensure customer access to IGIV. Essentially what it is, is to say it is a self-imposed restriction on sales that means that the current amount marketed under a sales contract with a distributor can't be altered upward, and it will ensure an adequate supply for all patients.

With that being said and I wanted to express those clarifications, I can move into the bulk of the presentation and here there will be another surprise for you considering we are discussing IGIV and the Critical Path, I have follow-on protein products. Now that I have your attention, the several workshops that have been held on follow-on protein products have elucidated certain industry concerns on both sides, whether you are talking about a follow-on manufacturer or "innovative" manufacturer. One of the major points of disagreement that has been discovered in terms

of the scientific workshops that have been held is the nature and capability of the current regimen of analytical tools that companies have at their disposal. A major point of agreement is that there does seem to be between the innovative camp and the follow-on camp and the regulators and stakeholders the importance of the FDA licensing scheme, appropriate research and development.

But while those of you who may be familiar with this debate and have maybe even taken part in it have probably found the scientific workshops to be somewhat more rancorous than what you would normally expect, I have to tell you that you haven't seen the worst of it yet and there will be more coming. But the analytical tools is something that I would like to discuss in greater detail shortly.

I just want to also show a little bit of crossover between several of the most recent FDA initiatives that have been coming down the pipeline. We can start with that right now--FOPPS and other programs and how PPTA views these

initiatives. There is a whole litany of interesting ideas at FDA, both CBER and CDER, have been coming out with and it includes process analytical technology, cGMPs for the 21st century, the risk-based approach, and so on. This is not just an FDA initiative. It seems to cut across all of the Department of Health and Human Services.

All of these programs have areas of commonality. In retrospect, I probably should have had a nice little diagram here. In the February FOPP workshop, Dr. Ajaz Hussain, from CDER, elucidated some important parts that CDER considers in terms of the Critical Path, and that is development of a common scientific framework for decision-making. Also, remember that he was talking at a FOPP workshop. The idea of the Critical Path is to reduce uncertainty; facilitate innovation; and take a systematic approach to the product life cycle.

We understand all of these opportunities and I have a few listed down here in terms of there being a lot of opportunities out there. The

problem that we are having is that the FDA has come up with so many that it has been a fast and furious release. I think that our industry in particular is having a hard time understanding where all these initiatives fit together, and integrating all of the initiatives to create some of the goals that the FDA has in mind. In short, the opportunity must be clear enough and well understood enough to have common areas such that the value to the industry can be understood by the industry, and can be acted on in such a way as to overcome the inertia. Objects at rest tend to stay at rest and if you have a system that is working it is very, very difficult sometimes to see the value of incorporating an entirely new schema to change the system that you have that is already working.

These are some more blurbs that have been given by CBER Director, Dr. Jesse Goodman and Dr. Kathy Carbone. Actually, I think Dr. Goodman's comments came from the Well-Characterized Biological Products conference and Dr. Carbone's came from the Science Board, both within the past

several months. Again, these show the linkages that we have and the areas of commonality in which we can operate as far as facilitation of new product approvals in terms of the Critical Path in biological products.

Some of the specific examples mentioned by Dr. Goodman in particular were viral inactivation and, actually #4 up there, the IGIV product development has been discussed in greater detail by Dr. Lamb this afternoon.

I just wanted to put this up to show that Dr. Janet Woodcock, from CDER, seems to have had a lot to do with coming up with the Critical Path and some of the other more cutting edge areas and has given these four very important areas in terms of how to think about the Critical Path in the FDA in terms of a public health initiative rather than just an initiative to get products out quicker and to help industry. It is important to realize that the Critical Path has very, very specific, very tangible public health benefits if we--we, as in the industry--are able to take advantage of it.

This last bullet, the disincentives that exist for the development of the therapies, this is sort of the policy umbrella under which I am

functioning as a policy analyst trying to interpret some of the initiatives coming out of the FDA. Basically, the disincentives have to be isolated and overcome, and we can only do that by focusing on legitimate areas for inquiry.

The one that we have learned and the one that we have polled our industry about that is singularly most important is the role of clinical trials in the Critical Path for product development. I wanted to thank Dr. Golding for his presentation on trial design and some of the other folks that presented this afternoon. I think it is a great concrete application of the things that I am talking about here on these slides. The clinical trial issue is one that has actually been characterized by FDA personnel as being one of overriding concern, and it is the most frequently mentioned comment that was given to the Critical Path docket, not just by PPTA or member companies

but by the public comment at large.

PPTA's Critical Path response--we submitted comments to the docket like many others did, and we actually used IGIV as an example of how to improve product development in Critical Path. I guess the most salient detail of this point, and just to reiterate what we had in our comments, was the fact that some of our member companies who have had very long histories with product development and product distribution and execution, and things of that nature--and I think Dr. Scott just alluded to this as well--have had to engage in fairly detailed and long clinical trials for something like a comparability exercise. We are of the opinion that this is not a value added activity and the focus should be altered to enhanced value without compromising safety.

Harmonization opportunities is actually another area of clinical trial design. Just briefly, I know that the NIH has come up with a Roadmap initiative that is talking about international harmonization. We actually have an

NIH speaker come to our Plasma Protein forum in June and they are going to be talking about harmonization of clinical trials as one of the three major initiatives in the Roadmap.

I am not going to read this. This is sort of a busy slide but this is our idea about adding value in terms of the long way that this industry has come in product safety, and we need to find new and better ways to get product to patients who desperately need it.

Just in summary, we agree with the rest of the industry about the utility of the Critical Path, and with Dr. Woodcock and other FDA personnel about the importance of clinical trials. We are happy to be here and I think this is an important venue, and we would like to thank the organizers for inviting us to speak. We look forward to discussing the next substantive steps and I think after the discussions that we have had we have some firm steps that we can take, and we can sit at the table and discuss these issues in specific and in an intelligent manner. So, thank you very much.

DR. SCOTT: I just want, obviously, to thank our co-sponsor, the Immune Deficiency Foundation and all of our excellent speakers, and

the people who are behind all of the planning, and this includes Rhonda Dawson who is our chief administrative person, my lab who got the coffee and did a lot of other useful things, also the medical advisory board of the Immune Deficiency Foundation, which includes many of the speakers who gave us very helpful input at the beginning, Dr. Golding and Dr. Goldsmith for their role in the planning committee, and the audience for your participation and interest, and the speakers for their many insights.

Very briefly, just to recap what we have, and I hope to post a summary of the workshop as well as the transcript and the talks on the FDA web site, first we heard about how far we have come in immune globulin and treatment of people with primary immune deficiency.

We also learned about the value of early screening for these diseases. We spoke a lot about

efficacy and it is clear that a lot of questions are still outstanding. That is, what is most important? Peaks? Troughs? Both? What is the best frequency of dosing? What is the best dose of immune globulin for these patients? And, what should be measured to determine this and to correlate with the clinical outcomes?

We learned that there may be gaps in antibody titers that might have an effect on some patients, in particular mycoplasma, ECHO virus, some of these infections that people get in the long term.

We also heard about the need to subset patients when you are thinking about efficacy in the field among people with fixed disease and people with new onset disease or without end-organ damage.

We also talked about the changing titers to pathogens and immune globulins, both the ones that are common pathogens and the emerging pathogens, and how to look at that and the potential utility of an IGIV bank.

We heard concerns from the Immune Deficiency Foundation about supply, and I think it is important for us to cover all the basis and to

understand where the disconnect is between the supply that is being put out there and the supply that is being received by patients. I think that we will work with the Immune Deficiency Foundation, and I am sure PPTA will as well, to solve any problems that are coming up.

In regard to the IGIV bank, I think it is important to link it epidemiologically forward and backwards, that is, as one member of the audience pointed out, to look at the collection, the geographics and the epidemiology of the donors as well as the epidemiology of the recipients and any infections that may be emerging there.

With regard to safety, I think we heard from the clinicians that it is difficult to know really how to compare products. We have heard that some concerns still exist but that in general most patients can tolerate these products very well, perhaps with some individualizing of

pre-treatments, infusion rates and so forth.

We also heard about the mystery of the allergic reactions with immune globulins, and I hope that people will come to maybe Don Baker to discuss this more. I hope the connections are made between the clinicians and the IGIV producers who have observed this problem so that we can investigate it further and, hopefully, fine the root cause.

We talked about active surveillance and passive surveillance and we learned just how much effort it takes to have an active surveillance. There are logistical challenges. There are also infrastructural challenges if you compare how our community of primary immune deficient patients is taken care of with the hemophilia treatment centers for example.

We also learned that there is a great economic challenge. This requires a lot of support. And, I think the outstanding question is what kind of surveillance would be best for our patients, in particular to be able to detect early

uncommon but serious adverse events in hopes of solving the problem.

Finally, we spoke about methods of paths to licensure, both currently and in the future, and hope for progress in that regard.

So, if anybody has anything they would like to add, if I have missed anything major, please do so now because we are going to be thrown out in negative three minutes. Thank you very much.

[Whereupon, at 5:30 p.m., the workshop was adjourned.]

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