agency's consumers, if you will.

Two of the four have been under for 18 months. I mean we are curious about progress. When you listed the issue of initiatives that can be reviewed, records and reports and recalls were items 11 and 12 out of a 15-item list. We are down quite a ways, and yet the whole algorithm really talked about this morning really requires going in and rapidly reviewing records and being able to--you know, the ability to generate a fast GMP review requires a good database, if you will, and Dr. Tabor was very clear about trying to bring people up to the speed where that is attainable, but it really highlights that tracking and records, which would seem to be rather basic management functions in a large-scale manufacturing process, need to be highlighted and need to be focused on.

It is easy to give reports on how that is going to public groups, even if it is to the BPAC in closed session. That hasn't been done. You heard Corey Dubin, our president, talk at some length, as a sitting member of this committee, about the need to FOIA, file Freedom of Information Act requests in order to see these consent decrees on the industry, you know, of which he is a consumer of the product, and, you know, having seen them, further questions get generated.

What about the reports that are required? Have

the consultants been hired? Are the reports coming in satisfactorily? What, if not? What is the sanction for a fractionator that is not in compliance with a consent decree, is the judge monitoring, is the judge educated to monitor, or it only an FDA process?

At what level in the FDA is a decision made about compliance with a consent decree that is ongoing? When you have Red Cross for six years, and it is one-half of the whole blood collection, how is it going?

I read newspaper articles about their new computer system, but what is the official report on the progress of the consent decree? I guess one thing you could say is are these permanent or are they to be expected? Would we be more likely to expect the other two of the four fractionators to go under consent decrees or for these two to come out?

I am not trying to be glib, I am just trying to say what is the hoped for status and what is the trend line in terms of attaining it, and I think a little bit more public disclosure would really be helpful in helping us see clearly the answers.

Thank you.

DR. HOLLINGER: Thank you, David.

Does someone from the FDA want to respond? Is there a public disclosure of what is happening with these

consent decrees and reports produced that is available?

MR. MASIELLO: In most of the consent decrees, there are--let me rephrase that--certainly in the blood consent decrees, there were time frames for reports, and there generally ended up being lots of communication on issues, but if the reports that are required are not satisfactorily completed, then, that would elevate the issue perhaps back to the court.

The question came up what is the recourse if people don't follow the consent decree. I am not a lawyer, but I can tell you that contempt would be one of the things that you would back to the court with, probably civil contempt initially, and it went beyond that, you might actually go to a criminal contempt action.

So, these reports--I guess there is an element there that you raise that is a good point, and that is, how can we communicate to you that these issues are being resolved, and it is something for us to take back and give some thought to how we can do that, because I think it is a good idea.

As we speak now, when an element in a consent decree is met by the firm, that information is not shared with the public directly. It may be available under FOI, but there are no affirmative statements that I am aware of that the FDA takes to explain that, and that is something we

can look into.

DR. HOLLINGER: Thank you.

Yes, Dr. Koerper.

DR. KOERPER: I have another question for you. Maybe you could explain to some of us who don't quite understand this. Consent decrees, are they time-limited or are they open-ended? Do they end after a certain lapse of time or do they end after certain specified requirements are met?

MR. MASIELLO: Yes, almost any of those can be the case. There are several kinds of injunctions. There are prohibitory injunctions where a firm might actually be closed down until all the corrections are made, and they are not allowed to open and ship products again until they are absolutely 100 percent.

Then, there are mandatory injunctions, which is pretty much the biologics area where you really can't afford to do that, because you are doing more harm by removing all the product from the market than closing them down.

So, you have established goals that they have to meet and you have time frames for that. Most of the current consent decrees have a sunset provision, I think of four or five years. That is not to say that in four or five years they are necessarily over. They are not over, Yogi, until they are over.

The Red Cross consent decree had a sunset provision of five years. As someone mentioned, it is in year six, and we are not at that point yet.

DR. HOLLINGER: Any other comments in regard to this particular item? Ms. Knowles.

MS. KNOWLES: I am wondering if it might be possible for this gentleman to maybe give us more information at a future meeting relating to the other issues surrounding the other injunctions for other blood facilities, just in terms of numbers, how many are still in that process, et cetera.

DR. HOLLINGER: Okay.

I am going to close the open public hearing and just to see at this point if there is anything in regards to the committee discussion and comments. Does anybody have an issues that have not been dealt with?

Okay. I think we are going to move on to the next item, which is supply and demand of plasma derivatives, a most important issue. Dr. Weinstein is going to give us an introduction and background to this issue.

III. Supply and Demand of Plasma Derivatives

Introduction and Background

Mark Weinstein, Ph.D.

[Slide.]

DR. WEINSTEIN: Better ways are needed to estimate

the demand for plasma derivative products. The need for this assessment has come about because of the shortage of certain plasma derivatives, particularly IGIV, and our difficulty in determining whether our efforts to alleviate shortages are working.

An accurate estimate of demand can also help FDA to prioritize activities to reduce shortages or to devote energies to other projects. The major objective of this session is to examine ways that demand can be estimated from the perspectives of manufacturers, marketing research expert distributors, and the patient community.

By way of background, severe shortages of plasma derivatives, particularly IGIV, began in 1997. Sporadic reports of IGIV shortages were received early in 1997, and FDA addressed requests for information from patients and physicians about product availability primarily by calling manufacturers to find out how much material they had in inventory and informing the requester about potential sources of product.

By November of 1997, however, it became clear that the availability of IGIV to patients was severely limited. In that month, FDA received hundreds of telephone calls about difficulties obtaining sufficient supplies of IGIV. The phone calls were from many different sources including individual patients and patient groups, physicians,

distributors, and major treatment centers.

FDA inquiries to manufacturers, large distributors, and group purchasing organizations revealed that nationwide there was little product in inventory or available on the market.

Major reasons for the shortage included decreased production related to achieving compliance with good manufacturing practices throughout the plasma fractionation industry, withdrawals because of CJD, insufficient manufacturing capacity, and an increase in demand for products both for FDA-approved and for off-label uses.

It is agency policy to attempt to prevent or alleviate shortages of medically necessary products as best we can given our legal authorities. We are committed to assisting and marketing and making sure there is an adequate supply available of product meeting high quality standards.

Each FDA center has a drug shortage officer who is responsible for investigating shortage reports to determine the extent and urgency of the reported shortage. The centers evaluate potential drug and biologics shortage problems, assess the potential public health impact, and propose steps to resolve such shortage issue.

FDA's primary means of identifying whether or not the shortage actually exists is to monitor and number and persistence of inquiries from consumers, manufacturers, and

distributors.

Another potential aid in estimating whether demand is being met is to determine whether the distribution of product is changing or remaining the same. Data about product distribution in the United States is supplied to the FDA on a monthly basis by manufacturers as part of the reporting requirement regulations found in the CFR.

Although these data do not give us real-time information or an accurate assessment of product availability in the marketplace, the data do provide information about whether the amount of product is tending to increase, decrease, or remain the same.

The next few slides will give you an idea of the nature of this data and its limitations in giving us a sense of whether sufficient supplies are available to meet demand.

[Slide.]

The data presented here show IGIV distribution data on a company-by-company and month-by-month basis in 1998. Each box represents the distribution of a single manufacturer. Although actual distribution figures for individual companies have been modified to preserve confidentiality, the overall trends in aggregate monthly totals are correct as represented.

The monthly distribution pattern varied widely depending on the manufacturer.

Some manufacturers of IGIV maintain a fairly steady state of distribution throughout the year, and you can see that in this white box, while others had reduced or had no distribution for a portion of the year, for example, this manufacturer stopped producing or releasing product at this point in time.

Other manufacturers tended to have a relatively low level of production during a portion of the year and then increased distribution considerably.

Therefore, the inability to meet demand for a particular manufacturer's product may not be reflected in the aggregate data for a total distribution of a given product class.

Reports of a shortage may reflect the inability of a customer to get a particular product brand. The shortage of a specific product brand may have effects beyond being merely a inconvenience, but have medical consequences, such as allergic reactions to alternative products.

Answering the question of whether demand is being met must take into account the degree to which product brands can be interchanged, as well as whether the product class overall is in short supply.

[Slide.]

Aggregate distribution data for factor VIII is presented in this slide. In contrast to IGIV distribution

which varied greatly month by month, the distribution of factor VIII varied relatively little except for some spikes as you see here.

The distribution pathway for these two products are also very different. IGIV is distributed mainly to hospitals, while factor VIII is distributed through home care companies and hemophilia treatment centers, thus, ways of assessing supply and demand and acquiring information about product distribution outside of the manufacturers' control are highly product-specific, and any sentinel system to monitor these products must be done on a case-by-case basis.

I have made estimates of demand for IGIV and factor VIII by extrapolating data from years when there was an adequate supply of product. Here you see an example of this estimate of projected demand.

For IGIV, I took the distribution data from 1996 and compounded that by an estimated annual growth rate of 10 percent. For factor VIII, I have taken the distribution data from 1997 and multiplied that by 6 percent, the average annual growth in distribution from the previous four years.

From these estimates, the shortfall in IGIV distribution was 25 to 30 percent for 1998, while distribution should have met demand for factor VIII. Yet, in fact, representatives of the factor VIII patient

community reported to the PHS Advisory Committee on Blood Safety and Availability in August 1998 that factor VIII was in short supply even though there was virtually no change in the overall aggregate distribution.

[Slide.]

At present, the demand for IGIV appears to be lessening somewhat based on the reduced number of requests that FDA has received for information about product availability even though the distribution data shows relatively little overall change, that is, they are still well below this projected level of demand.

This may be the result of a feedback effect of supply on demand whereby the high cost and past unavailability of IG reduced off-label use and inhibited the development of protocols for new uses.

Thus, in one sense and by one measure, demand has been reduced, but this clearly does not mean that the desire for IGIV has been met or that the health needs of the American public are being adequately addressed.

Exploring how demand should be measured is one of the reasons for placing this topic on the BPAC agenda. Also, the PHS Advisory Committee on Blood Safety and Availability directed its staff to develop options to be presented to the Blood Safety director for the creation of a sentinel system to monitor production, demand, and

utilization of good products, and to create projections for future demand. Our efforts at this meeting will help to examine the feasibility of creating such a sentinel system.

Dennis Jackman and Ron Demarines, representatives from the International Plasma Products Industry Association, and Georgetown Economic Services, respectively, will speak about legal restraints that manufacturers have in sharing information about supply and demand publicly, as well as ways that they can assist us in addressing the problem of estimating demand.

Patrick Robert from the Marketing Research Bureau will talk about methods he uses to estimate short and long term demand, particularly of IGIV.

Patrick Schmidt of FFF Enterprises, an organization that manages the distribution of plasma derivatives, and Allan Dunehew from Premier Purchasing Partners, a group purchasing organization, will present their perspectives on the demand for plasma derivatives and potential indicators of demand.

Finally, Patrick Collins and Tom Moran, representatives from the patient user community, will talk about product shortages particularly the differences between needs and wants, and the ways the user community may help us estimate demand.

Are there any questions?

[No response.]

Perspective on Supply and Demand of Plasma Products

Dennis Jackman

MR. JACKMAN: Good afternoon, everyone. My name is Dennis Jackman. I talked earlier.

[Slide.]

I am from IPPIA, International Plasma Products Industry Association, and our members include Alpha Therapeutics, Bayer, Baxter, and Centeon, and we are happy to be here to talk about understanding a little bit about supply and demand to provide some perspective on that. That is what we were asked to do.

[Slide.]

First of all, we understand that stakeholders have a strong desire to really understand supply and demand for a variety of reasons, and we understand the need for information, the desire for information. In fact, the Association provides what we think is useful monthly data on U.S. distribution, and I will talk about what that means in terms of demand.

We also, as manufacturers, are very interested in trying to meet supply. That is the goal of manufacturers, to meet supply and meet patient needs.

[Slide.]

I think some of you have seen this data before.

This is data that is provided monthly. It is in a tabular form, as well, but I am providing the summary charts here. It shows U.S. distribution versus inventory over time. This is for IVIG.

What you are seeing, these are monthly data, we are well below one, which indicates that our average inventory over time is well below one, which means we have well less than a month's supply. The last month, in fact, for instance, was about three-tenths of a month's supply on average.

It is not an absolute predictor of demand, but to use an FDA type of word, it is sort of a surrogate endpoint. It sort of shows that over time, that we keep being at a relatively low level of inventory over distribution over time, which indicates there is tight supply situation. It is not a perfect estimation of demand, but it's an estimation.

We want people to recognize that we are providing information that could be useful, and we distribute that widely. That is one thing.

[Slide.]

I talked about the monthly trend data. We also have, in terms of supply, some people have asked whether we can project supply as an association, and the answer is we really can't. We got a legal opinion from outside counsel,

one of the top antitrust firms in Washington, that made it very clear that it is illegal for an association in any way to facilitate the exchange of information on projecting supply or for us to project supply.

Saying that, again, we are trying to collaborate in any way we can and cooperate by providing our monthly data, but we can talk about what impacts future supply, and we do think that future supply is heavily impacted, of course, by our investment in plant capacity and new processes, and that is how we are trying to meet the supply demand, but also regulatory actions.

Regulatory actions have a major impact, actions like, for instance, today, the post-donation information decision will have an impact on supply. There are other regulatory actions, as well, product and process of plant approvals, how rapid will those be, when will they occur. That will have an impact on supply.

Compliance actions, those will have impacts on supply. Those are very hard to predict with any accuracy, but that gives you some idea of the factors that affect supply in the long term.

[Slide.]

Turning to demand, first of all, as I mentioned, we produce this distribution data. I want to make it clear that it is consumption data in a sense. It is distribution.

It is not demand. Demand and consumption are two different things.

There may be pent-up demand or unmet demand in the marketplace, and there are many indications that that may exist. So, what we have is distribution data.

The trend data does give you some ideas, as I described earlier, on predicting demand, because you can sort of see if you are on balance meeting that consumption. If your distribution or your inventory is not building up, you are probably just meeting demand or undermeeting demand.

There are a number of demand measurement challenges I would like to talk about, as well, and I think other people are going to address those. First of all, demand of our products is affected by a multitude of variables, it is prescribing, it is usage, it is reimbursement, as well.

If you have a demand for a product and the reimbursement isn't there, that demand may not be met. So, a demand curve is always based on a given amount of demand at a given price, given certain amounts of reimbursement, and if reimbursement doesn't exist at a certain level, then, it can affect the demand.

Those are hard to measure, and they are challenges. Costs are another thing that could impact demand, as well, cost of the products, and of course price

of the products.

So, I think we have some reliability issues in trying to project demand. At a macro level, having some general ideas of where our demand might be going could be useful, but I think everybody has to be aware of what the limitations are in terms of reliability and its usefulness as a predictor or certainly we think there are several limitations on that type of thing and predicting regulatory action or in any way trying to target regulatory action toward where they feel there is an imbalance of supply and demand.

We think there are so many limitations with the data that that may not be the best way to go.

[Slide.]

The summary is our goal really is to meet patient provider needs and demand. We feel that estimating future demand does not ensure that the demand will be met, and that is stating the obvious. It may provide some useful information, but we want to do things that really would try to help us to meet demand.

Individual companies and members of our association are all robust competitors. They are going to seek to meet demand. Every textbook model, we have all had our Economics 101, every textbook model shows that given a certain amount of revenue possibilities, certain costs, the

competitors will seek to meet demand, and they will succeed in meeting that demand officially.

There is no more efficient market than the U.S. market. Any type of proposal with the try and tune, and match up supply and demand at a federal level and then try to pick federal actions on that basis, I think probably are not going to be that successful over time.

I think that most fruitful would be policies that would optimize our ability to meet that demand, and that means reimbursement, again, hopefully, we will have reimbursement policies that are in place that will allow patients to have their demand met, if the physician prescribes a product, that they can obtain it, because we have adequate reimbursement.

Secondly, an improved cGMP environment. That means that we are working with the agency. We just had a GMP workshop in May to try to improve our common understanding of GMP requirements and take those back to our plants, and continue to enhance our training and our investment, and trying to meet GMP, and that will help us to meet supply and demand.

Also, product and process approvals. If there is anything that we could do, and again, I think this is a group and team effort, all the stakeholders have to be involved, but to improve the product and process approval

requirements, clinical trial requirements, review requirements, and achieve that balance, the optimal balance between cost-benefit, that will help us to meet demand, as well.

Thank you very much.

DR. HOLLINGER: Thank you.

DR. EPSTEIN: I did have one question for Mr. Jackman. As you well know, the FDA does not have authority to control exports.

We treat export of products the same way we treat interstate commerce under our laws, and yet it is a fact that only about half of the plasma collected for fractionation is utilized to satisfy the U.S. demand for plasma derivatives. The other half is presumably exported and used in other countries, and also some portion of the finished products of manufacturing by U.S. fractionators ends up in export.

I would just like to ask you, and recognizing that the majority of large U.S. licensed fractionators are in fact not U.S. owned, I would like to ask you how does your industry look at the issue of whether there is some moral obligation, not a legal obligation, but a moral obligation to satisfy the U.S. need from the donations that are obtained in the U.S.? In other words, recognizing that there is a twofold excess of collection relative to the U.S.

need for endproducts, why are we ever in a situation of inability to supply the U.S. need?

I would just ask how do you look at that issue?

MR. JACKMAN: I would be happy to answer that question. First of all, we are, in terms of IVIG because we are talking about IVIG here very heavily, there was testimony given, I think it was last year, that showed that about 80 percent of the IVIG stays in the U.S. market, and about 20 percent of it is exported.

We also are importing about 20 percent, as well, so there seems to be pretty much a balance there. I think anybody would indicate that the most efficient way for world to work is to have mobility of goods and mobility of therapies, because where the needs are greatest at one point may change over another point.

We may at some point need a European manufactured product to satisfy some of our need. As a matter of fact, there are products that are available in Europe, in fact, some of them, we have their applications pending at the agency.

I think a perfect example of helping to meet supply would be Endobulin. There is a product that is produced by one of our companies, Baxter, that was mentioned at an HHS hearing about nine months ago. It is being sold in Germany and a number of countries, and the company would

like to bring that in the United States. So, there is as an example where if we could act promptly on that kind of an application and get that product here, we could bring it right into the country, and that would really benefit our supply situation. It shows that mobility of goods both ways can be very beneficial.

In terms of other products like recombinant factor, those type of things, there is every indication, I have seen some data out there that show that the U.S. population is getting--if you did it on a strictly proportional basis--the U.S. population gets more than a proportional basis of the products, way more, and we could take about some of those data, but I have seen some data to indicate that.

So, I don't believe that the U.S. is being disadvantaged, in fact, I think that on the recombinant factor side, for instance, you want to make it so that it is beneficial for us to both manufacture here and distribute here, and meet the demand here, and we are trying to do that, and there is indications that we are doing that.

At the same time, if there is demand that has to be met overseas, you are going to try to meet that, as well, because after all, some of those patients have no other choices for therapies. So, that is a moral obligation, too. We consider it a moral obligation to supply patients

throughout the world, and I think that is a moral obligation.

DR EPSTEIN: I appreciate those remarks. I think there is perhaps opportunity for some misunderstanding in that the products that you are calling imported are still fractionated from U.S. donations. These are, for example, the recovered plasmas.

MR. JACKMAN: I am talking about finished products.

DR. EPSTEIN: I know, but the ones that are imported into the U.S. by U.S. licensed manufacturers abroad are still fractionating U.S. plasma.

MR. JACKMAN: But Jay, actually, the situation is we don't have right now at this point, the United States does not have a shortage of plasma in terms of producing what we could do, our plants could run at capacity with the plasma we have, where if there were a shortage of plasma, that might be an issue, but it is not an issue. We are running at full capacity.

Actually, if we could let our plants run fully and get them up to full production with a predictable environment in terms of compliance and all those, if we could optimize that situation, we would help to alleviate the supply situation in a great way, and if we could get more rapid product approvals on some of the process--in

fact, for instance, there was a process approval application, there are several others in there that could increase yields of plasma by up to 40 percent.

So, rather than worry about if the plasma is moving to other places, when the U.S. demand has already been met, or U.S. manufacturing needs have already been met, let's think about how we can get greater yield out of a liter of plasma. That would be I think the most fruitful discussion.

DR. MITCHELL: I still don't understand what you are saying. On the one hand, we are saying that there is a shortage of IVIG in the U.S., but you are saying that there is full capacity of the manufacturing plants, and therefore there is no problem. Is that what you are saying?

MR. JACKMAN: No. What I was saying was in terms of plasma, the question was about exporting plasma, whether or not plasma is being exported, we don't have a problem in the manufacturing side in getting the plasma we need to produce the IVIG we need.

What we have is that there is some temporary production interferences or interruptions as a result of some of the activities in terms of trying to achieve full compliance with GMPs. So, that is the situation there, but we have to make sure we are talking about, you know, it's apples and oranges.

DR. MITCHELL: So, you are saying that you are not exporting IVIG or producing IVIG from U.S. donations that are being sent to elsewhere in the world?

MR. JACKMAN: No, I am not saying that. I am saying that we are producing IVIG that is being exported, but at the same time we are bringing back in product that is a net sum, zero sum gain, but the issue isn't plasma, the issue is enough product coming out of the plants.

DR. MITCHELL: You agree that there is an IVIG shortage in the U.S.

MR. JACKMAN: There is an indication that we--yes, there is an indication that we are on--there is not much inventory in the pipeline versus supply, and that there is probably demand that goes beyond that. I think that IDF will talk about that in more detail, that there probably is additional demand that is out there.

But we are manufacturing basically all that we can right now given current limitations. We are exporting some and importing some. If you were somehow to say let's not export that small amount that we are exporting or that amount that we are exporting, then, what would happen to those imports?

DR. MITCHELL: So, you are saying that the amount that we are importing from blood sources in Europe or from blood donors in Europe is equivalent--

MR. JACKMAN: Again, the point of the matter is that the amount of finished product being made available in the United States, when you compare our exports to our imports, is basically a net sum gain, whatever the source of the plasma is. To me, the issue isn't the source of the plasma because we don't have a shortage of plasma right now.

The point is that we are importing as much finished product roughly as we are exporting. So, in terms of the actual finished product that is available to consumers that are in there, that is a net sum zero.

DR. HOLLINGER: But if you wouldn't export that amount, you would then have enough for inventory.

MR. JACKMAN: You know, there is a market situation here. If we try to limit that in some way, what would happen then to that manufacturer who is now currently selling and exporting to the United States, if all of a sudden, we then say, all of us, we are not going to send any of that overseas to sell to some of those customers and markets overseas--and some of those are Canada, by the way, I think there is some agreements with Canada and requirements that some contractors have, and there is an obligation because they don't fractionate there--but what would happen then?

I mean would that mean that all of a sudden--I can't predict this because we haven't had that conversation,

but you have to think about some possible unforeseen consequences. In that situation, that manufacturer may say well, that supply is now remaining in the United States, now there is a gap over here, I will just sell it over here.

I mean the world works that way. Where there is demand, manufacturers will try to meet that demand, and to try to sit here, either as a committee or an agency, and try to carefully plan where a product goes and where it doesn't go, it hasn't seemed to work very well in many centralized planned economies.

I wouldn't recommend we got that direction. I think what you wind up doing over time is you wind up discouraging potentially investment in the United States. If the demand is overseas at some point, you just basically are saying why don't you just invest in other places, if you can't have the free mobility of your goods.

You are encouraging, you are basically discouraging investment in the United States. So, there are a lot of consequences to those kind of behaviors. In fact, Secretary Shalala, in a letter in response to the Advisory Committee on Blood Safety and Availability, in response to a question about whether there should be any kind of limitations on exports said as much as I understand the desire to supply the U.S. population, she did not feel that the idea of in any way limiting exports was a wise idea

because it has so many unforeseen consequences.

It has been tried the past, it hasn't worked, and you probably will wind up doing more harm than any good. So, what I would like to turn back to is let's look at the regulatory policies that we can implement that would help us to meet the demand as manufacturers.

Let competitors try to meet the demand by improving the regulatory environment by accelerating approvals, by looking at surrogate endpoints, by looking at clinical trial requirements. There are processes out there that could greatly increase the amount of supply if they were acted on as quickly as possible, we would see no problem with supply, and supply and demand would be met, and we wouldn't be worrying about exports.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: Is the average price per gram for IVIG in Europe higher or lower than the United States?

MR. JACKMAN: I don't have data on the pricing in every single country, but I have asked people what is the marketplace out there a little bit. It varies country by country. In some cases, the European price might be higher, in some cases the country price might be lower.

The U.S. is not always the highest, and sometimes not the lowest. The interesting thing is we have had some complaints from European patient organizations that are

starting to say, gee, we don't even want you to export the product you are sending, we don't want to see European product going to the United States for a higher price. That has actually been said.

So, we have people over there, other advisory committees and other advisory groups trying to say, look, why don't we try to hold back here. That is all we need in the world is to have a number of committees sitting here trying to say let's hold everything here, let us control the market, we are smarter than the marketplace. I don't think that is going to work.

DR. MITCHELL: So, is there a shortage in Europe also, and is there a sense that it is the same magnitude?

MR. JACKMAN: I don't have a sense of the supply and demand balance in Europe. I have heard, I think at a recent symposium, the representative of one of the patient groups there that uses IVIG indicated that he felt there was a tight supply in Europe, as well, but I can't give you an absolute accurate assessment of that situation.

DR. HOLLINGER: Dr. Fitzpatrick.

DR. FITZPATRICK: At the last meeting we discussed clinical trial design and how that could be used to speed up and help alleviate the shortage. Has there been any progress? It has been three months. That was supposed to be a more rapid way of looking at this?

MR. JACKMAN: We would like to see progress in that. I am sure people may want to comment on that, but we think that there is room for progress clearly. I know that they are working on trying to come up with some clinical trial requirements, new clinical trial requirements for new IGIV product, for instance.

At the same time, we have had applications pending out there. I don't want to comment on the particular merit of the application. That is open to discussion, but when it is taking a certain amount of time to do that, you just have to look at it and say are there any ways we could accelerate that.

Are there ways, for instance, we could harmonize applications between Europe and the United States that might help us to accelerate that when you are trying to bring a product in from Europe, that we could have that kind of harmonization.

Are there ways to develop surrogate endpoints? I know that is being looked at by the agency for IGIV. When you have a new process for a product, does that require a large clinical trial, treating it as if it is a brand-new product, when, in fact, it is still IGIV, does that require a full-blown, large-scale clinical trial, or can it be done with surrogate endpoints and with a smaller n? All of those kind of things.

By the way, all the manufacturers in the association play user fees, so under PDUFA, the User Fee Act, there are supposed to be timelines as to when things get acted upon. When an application takes place, there is a clock that starts ticking, so trying to adhere to that PDUFA timeline would be helpful, as well, on a number of applications.

DR. GOLDING: Could I just comment in relation to the previous question and some of the comment that Mr. Jackman made earlier? My name is Basil Golding. I am from the FDA.

The question of foreign suppliers sending in applications to the United States and asking for approval for use of their IGIV, this is being looked at by the agency in a manner at to try and expedite those reviews as quickly as possible, and there have been multiple meetings and a lot of time and effort devoted to that, and I think you are probably aware of it, plus the trial design issue has been a major discussion point between the agency and the IDF and manufacturers, and this is an ongoing process.

I think many steps have been taken in the right direction which will speed up the trials and the approvals, so I think as far as from our perspective, I think it is fair to say that everything is being done or much is being done to try and approve more IGIV as quickly as possible and

to make sure that the FDA's part in this equation is to optimize the process.

MR. JACKMAN: That is great to hear. As I mentioned, I know that some actions are being taken. I think in response to the question, a review of everything possible that could be done, and including a review of FDAMA, the FDA Modernization Act, and its application to our products would be useful, accelerated approvals. Those are envisioned for biologics. In a supply shortage situation, it is clearly envisioned under FDAMA as one of the areas we should be focusing on for accelerated approvals.

It is not just the AIDS drugs and protease inhibitors. It is where we have a population that could use the product. FDAMA clearly applies, and i would be happy to share more of that information.

So, if we could work and maybe have a symposium where we could explore what the possibilities are, and make sure we are doing everything possible to optimize the approval and review environment, we would welcome that.

I know that has been talked about a little bit and it is something that we would envision being happy to do, and I think that could have some positive results. It won't be immediate, but in some cases, some of these product applications would be an immediate impact.

DR. HOLLINGER: Dr. Ohene-Frempong.

DR. OHENE-FREMPONG: Are you suggesting that if the approval regulations were streamlined somehow, that it would be easier than to import finished product from Europe to meet the demand in the U.S.?

MR. JACKMAN: That is one side of it. I am not just talking about the European imports, but I know for a fact that there are some applications or at least an application, and I mentioned one product Endobulin, that is being sold in a number of European countries. The application is pending, and if that were approved--and there may be reasons why it hasn't been approved yet, I know they are working on it--but the fact of the matter is there is a timeline.

This was talked about nine months ago, so the sooner that gets approved, every month that goes by, that Endobulin is not in the marketplace, and that Endobulin will have a significant kick to the IVIG supply, and the manufacturer is anxious to import it and anxious to sell it to meet demand.

So, we are talking about projecting demand and trying to estimate, well, we know that the demand is there, it is a matter of let's get the product in. So, that would help there.

Secondly, it is not just that. There are process applications and things like that are being talked about,

that if those process applications were approved, and every month it takes--let's put it this way--every month longer it takes to approve that, we don't get the benefit of that new process, and one process would increase the yield from a liter of plasma by well over 30 percent.

So, think about what the implications are of that process if it gets reviewed rapidly and approved on the IVIG supply situation. I think that is where the most fruitful focus would be, and we are willing to engage in this in every way possible, make constructive suggestions and work with government, the decisionmakers.

DR. HOLLINGER: Mr. Demarines.

Ron Demarines

MR. DEMARINES: Thank you very much. My name is Ron Demarines. I am with Georgetown Economic Services.

Let me give you a little background on Georgetown Economic Services, GES. It is a research firm that designs and implements market research, both domestic and foreign.

We provide market analysis for a variety of clients including trade associations, industry coalitions, lobbying groups, and corporate clients in a variety of industrial, consumer, and agribusiness products.

GES has years of experience in conducting surveys to evaluate the overall health of an industry by tracking economic indicators, such as shipments, consumer and

industrial demand, profit levels, employment capacity, cost of goods sold, a number of a variety of other indicators.

We also provide analytical suppose for industry groups in their dealings with government regulators. In this capacity, GES provides analysis of the economic impact of government regulations including environmental, trade, and worker safety regulations.

I was asked her to come here to describe the process that we envision to measure demand for several blood derivative products, especially IGIV and factor VIII. I have to tell you that I am not an expert in this industry. We are certainly expert in measuring demand.

As I understand the current market situation, the rate of demand growth for IGIV and factor VIII has led to periodic shortages in the two products. In some way, the blood derivative market is very much like a traditional commodity market that we dealt with at GES.

There are several layers of distribution between the producer and the end user. There is a spot market operating alongside a long-term contract market, and the uses of the products, new uses are constantly being developed, creating a new demand for the product.

But unlike most commodity markets, applications of some of the products in this industry, in the blood derivative industry, may be expanding at a far greater rate

than could be envisioned just a few years ago.

Predicting current and future demand for these products is a challenging task. The obstacles include unpredictable, long-term applications of the product, especially in off-label applications, and the lack of a comprehensive and centralized body of data on current usage.

In addition, the demand for these products is highly inelastic, and that is, there is very little correlation between the quantity of products purchased and the price of the product, and there are also very few substitutes for these products.

Therefore, traditional indicators of demand don't come into play here to the degree that they would in some traditional commodity-driven market. Some of these indicators would be days of supply in the pipeline, order backlog, and spot versus contract price. So, these would not be able to be used effectively as an indicator of demand in this industry.

In arriving at the level of current demand for these two products and projecting future demand, an understanding of the market dynamics is needed. In this respect, the most valuable source of demand data would come from the distribution channels.

To calculate demand, hard data must be gathered from the distributors, other middle men, and the health care

providers.

[Slide.]

Most of you probably cannot see this, but this is the various levels in the distribution channel for these products. As I said, I am not an expert. You will notice that I have mislabeled IVIG. I put IVIG. We didn't catch it, but it's IGIV. Sorry about that.

The group purchasing organization, because as much as 80 percent of IGIV sales are made to group purchasing organizations, GPOs, this group of companies will play a key role in demand calculation.

I envision a survey designed to gather the level of purchases and sales over at least the past eight quarters. Data on sales intended for FDA-approved usage, and off-label usage should also be captured from the GPOs to the extent that they can provide that information on this subject.

Questions regarding pricing to the next level of distribution should also be gathered in this process.

The next group is the wholesalers. Because the wholesalers are positioned between the GPOs and the next level of distribution, their insight should provide a valuable information on the demand for these products.

Since wholesalers distribute as much as 80 percent of all prescription drugs, as I understand from the research

that I read recently, this group of companies should provide further information on the trends in sales for FDA-approved usage and off-label usage.

This group should also be a source of information for future demand for the blood derivative products because they tend to be further down the supply chain.

Data provided by dealers, the next level, will provide still further awareness of the current and future demands in the marketplace. Because this groups serves the spot market, the level of sales gathered from the dealers should provide an additional level of data for calculating current and future demand.

Finally, in the distribution chain, the home health care segment. They report a 20 to 25 percent of IGIV and more than 70 percent of the clotting factors. This group is perhaps closest to the end user and should be a valuable source of information on the demand and current and future of the blood derivatives.

In addition to the research surveys and interviews in the distribution channel, we would further suggest doing a series of interviews with medical researchers from, for example, the National Institutes of Health and other appropriate agencies, as well, selected biotech firms, also researchers and scientists employed by IPPIA could provide additional information and background material on new uses

for the target products.

Other sources of information include the Immune Deficiency Foundation and the International Patient organization for Primary Immmunodeficiencies or the National Hemophilia Foundation.

The objective of these one-on-one interviews is to probe into the most recent research on off-label usage for these products and to assemble some degree of consensus as to the future demand for the application.

[Slide.]

Based partially on this information that I have just described, we will suggest putting together a demand scenario for a one-year, three-year, and five-year period.

What I have up here is basically a table that describes how we are going to take the data, how we would envision taking the data from the information we have gathered, and putting it into a demand formula.

The demand calculation will be further shaped through projections of usage for both FDA-approved applications and off-label applications. For example, an analysis of the immune deficiencies requiring FDA-approved IGIV or factor VIII treatment should be undertaken to determine the percent of the population with these deficiencies.

This analysis will likely be based on survey

results, one-on-one interviews, and a review of the published medical research. One-year, three-year, and five-year projections of demand should be constructed by examining U.S. population growth, the projections for this population growth relative to the level of individuals with immune deficiencies, the average annual per-patient amount of IGIV or factor VIII given as treatment for each of these types of deficiencies should also be factored into the calculation.

Of course, other factors enter into this calculation, such as duration of the treatment and the age of the patients, et cetera. The same procedure should be utilized for off-label applications and the same types of projections would be based on these types of calculations.

I was told to keep the comments brief, so I did, and if you have questions, I will be glad to try and answer them.

DR. HOLLINGER: Thank you.

The next discussion is going to talk about background considerations for the estimation of IGIV demand. Mr. Patrick Robert, president of the Marketing Research Bureau, Inc.

Background Considerations for the Estimation of IGIV Demand

Patrick Robert

MR. ROBERT: Good afternoon. My name is Patrick Robert, Marketing Research Bureau. Our firm has been involved in collecting data for the blood industry a few decades.

[Slide.]

On the first overhead is a presentation of the sales of IVIG since 1981, shown in 2.5 grams units, so as you can see, it has been fairly steady growth. It's about 8 to 10 percent growth per year except for 1997, where it started decreasing following the events which we have been talking about today. I believe that you have heard about 1998 and 1999 where the growth has been negative again.

So, this is a reflection of the very great success of polyvalent IVIG or IGIV, as you prefer in this country as well as in other countries, as well.

In 1995, our company undertook a forecast study to attempt to determine what would be the demand for IVIG in 2000. I apologize if there is some overlap with the previous speaker, but many people are interested in knowing the same thing obviously.

This study was completed. Obviously, it was done four years ago, so it is somewhat out of date, but back then in late 1995, we predicted the market to be about 18 metric tons by 2000. If I am not mistaken, in 1998, approximately 15.5 metric tons were used in this country, so the growth,

the demand is still growing.

[Slide.]

Now, our methodology is strictly going from the bottom up, and we first went to the medical literature to see what medical indications were used, for which medical indication IVIG was prescribed, and this is just the beginning of one updated list of such indications, which were used for an update of the study, which we will begin soon for completion by the end of this year.

The way we do is to ask the end users, that is, the prescribers, the physicians, and also ask them questions about alternative therapies, possible changes in dosage, what is the impact of cost and reimbursement, and, of course, the impact of access to the product, and we combined this with all kinds of demographic and economic and social data.

So, we hope to be able to update and come up with more reliable figure for a forecast of the demand for IGIV in this country by 2004, whatever, 2005, three-year horizon. So, this is what we do in this country, and we do similar work in other countries, and that is pretty much all I have to say today.

Thank you very much.

DR. HOLLINGER: I am not sure I understand how you got your figures. I mean of 14 metric tons in 1997, and so

on, where did that come from?

MR. ROBERT: This is rather complex methodology, which I don't know if I have time to explain here, but we go to the number of patients which received the product by medical indication. We apply a dosage or we know the dosage which translates into grams.

DR. HOLLINGER: Where do you get the number of patients, for example?

MR. ROBERT: The number of patients is actually provided by a supplier of data, which I understand uses some government data to start with, number of patients hospitalized with certain medical conditions. I think there is national health surveys, and these type of data.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: I would like to follow up. The health interview survey doesn't include some of the things that are up here. Did you use that or did you go to physicians and other providers to identify the various conditions you are talking about?

MR. ROBERT: I mentioned the national health survey. This is probably not the right term, but there are all kinds of databases supplied by the government, but, in fact, I did not use these data directly, but these data as processed by another supplier, which I updated and reformulated the figures, and completed the figures for my

purpose.

DR. BOYLE: There is good news and bad news here. The good news is that your figures are widely quoted, and they have been quoted in a number of the projections about demand and supply and demand. For that reason, I think we are all very interested in a fairly detailed understanding of how you got to where you got.

Did you interview a national sample of providers to estimate what they were doing? Tell us what you did.

MR. ROBERT: As I said, I don't know if we have time to go into detail, but yes. I interviewed a number of opinion leaders and a number being about 25 back then, which is not many, but that is the number, and we also undertook a mail survey among several hundred physicians who prescribe IVIG, so as to balance the responses from both groups.

DR. BOYLE: Do you mean you received several hundred questionnaires back from those who were treating?

MR. ROBERT: I sent out several hundred. I did not have a very good response, I must confess.

DR. HOLLINGER: Dr. Fitzpatrick.

DR. FITZPATRICK: I would like to go back to a previous question. Could you give us an idea of what the supply issues are in Europe, and is there a shortage in Europe similar to what we see here in the U.S., and is the monthly supply, is there less than a month's worth of supply

available in Europe, or is the supply in Europe different?

MR. ROBERT: I am sorry, I don't have monthly supply data on Europe.

DR. HOLLINGER: Dr. Verter.

DR. VERTER: If I can follow up on where I think Dr. Boyle was heading. Is there anyone in the room who knows, one, how much is manufactured in the United States in 1998, what the total manufacturing was? If you know that, is there anybody who knows how much was sold to intermediaries? The last question, which I am sure no one knows is how much was actually used by the individuals?

I think we have heard in previous reports of this committee that it is very difficult to get good data because even the doctors who service these patients don't often know how frequently they use it, how much they use it, so it is self-regulated by the patients from I think what Dr. Boyle and others have told us in previous meetings.

I don't have any concept other than what I hear constantly that there is a shortage. I don't know how to quantitate that shortage, and I have never heard any data that gives me an insight on how to quantitate it.

MR. JACKMAN: I will try and answer that question. In 1998, it was approximately 15,000 kilograms of IVIG manufactured and distributed in the United States. Most of that goes through intermediaries in some way, shape, or

form. In the broad sense of the word, intermediaries, home health care companies, a number of people like that, that would distribute it. It does not go directly to consumer.

DR. MACIK: I am listening to a lot of talk about demand, but do we really have any idea of what the demand is? It seems like we are using a lot of formulas about how much you sent to distributors and what was happening, but I mean can't we go to an individual hospital or--I mean somebody wrote a prescription for that patient to get IVIG. How many prescriptions were written in a year?

There should be some way that we can tabulate what is happening to know what is going on here, because it doesn't seem to add up between where product goes, and yet the end user saying they can't get product.

I realize that marketing is a very complex process for a poor clinician to understand, but somewhere, somebody prescribed a drug, and the patient is using the drug, and somebody is bringing to his home, we can't get an idea of who much is actually being used.

DR. KOERPER: Usage does not equal demand. I think that is part of the issue here. We may write prescriptions for 25 grams of IVIG, but there may only be 20 grams available, and that is what the patient gets that month, or the patient may skip a month or the patient may have to go for five weeks instead of four weeks.

So, simply tabulating the prescriptions or what was actually administered doesn't capture what it is that physicians would like to have given under optimal circumstances. That is the intangible that we are having trouble getting ahold of.

DR. MACIK: I understand that. In fact, that actually was my point. I mean do we really know what the demand is because we don't even know how much we are giving out. Nobody can even tell us how many prescriptions we have written, whether or not they were met. Even if we assumed that they were all met, we don't even know how much that is.

Then, it comes to the second point, which is what you are saying, is do we know how much of that was actually given. At some point, you know, in hemophilia, we have our patients keep a log of how many units of factor did they infuse. You add up all the logs, and you get some idea of what was used, and then you can go back and say how often did you not give yourself an injection when you thought you might have.

There seems to be something kind of lacking between trying to get some information about what is out there and what true demand is.

DR. KOERPER: I think the endpoints aren't quite as finite with the use of IVIG as they are with hemophilia. In hemophilia, patients bleeding now, he knows if he needs a

dose now, he knows if the bleeding stopped if he gave himself enough or it didn't stop and he has to give a second dose, he knows right away, whereas, with IVIG, the intangible is did the patient more or less infections over the course of a month, and it's a little hard to have an immediate cause and effect, the way you can in hemophilia.

DR. HOLLINGER: So, we know basically, if we take the numbers that were listed here, we know how much is manufactured, but what you are saying is that actually, the prescriptions might have been written for 25,000, and only 15,000 is available to use. That is the issue that we don't know.

Does anyone here know how much is used off-label, the percentage that is used off-label, do we have any approximations?

DR. GOLDING: I don't think there are accurate figures for this, but many leaders in the field from large medical centers that were asked this question said in the region of at least 50 percent of the use was off-label. I think the IDF also believes that this is the ballpark area of off-label use.

DR. HOLLINGER: Thank you.

DR. KAGAN: I just want to make one brief comment. At our university hospital, our Pharmacy and Therapeutics Committee has come to those of us who use it off-label, and

said you are out, you wouldn't even possibly go on the list at this point for consideration. So, orders from our hospital are really being limited to those where there are true indications, and the off-label people aren't even getting the chance to write the prescriptions or write the orders for the patients to have it in the first place because it's such a low priority given this apparent shortage.

DR. HOLLINGER: Thank you.

The next discussion is on The Impact of Distribution on Supply and Availability: A Premier Model. The first discussant will be Patrick Schmidt, CEO of FFF Enterprises, Inc.

The Impact of Distribution on Supply and Availability: A Premier Model

Patrick Schmidt

MR. SCHMIDT: Thank you very much. It is a pleasure to be here.

[Slide.]

Listening to the last few minutes of conversation, I was struck by the observation that we have had over the last several years, that this is an industry that is starving for data. It is very difficult to come by, and I don't know if we can answer some of those questions, but we are certainly going to give it a try.

[Slide.]

A little bit about FFF. You have probably never heard of us, but our corporate mission statement is called "Helping Health Care Care." There are a lot of abuses that take place at the blood products distribution market. I may have time to touch on those for a minute, but that is our corporate vision.

[Slide.]

Our corporate mission statement, I will just focus on really the key words. Everything that our company gets involved in has to do with availability, affordability, and safety of crucial products, and we try and create innovative distribution systems, and those innovations have come from our customers.

We consider our customers the manufacturers of these products, as well as the end users, and every innovation that we have been credited with has been a customer-driven innovation.

[Slide.]

FFF was started in 1988, a little more than 10 years ago. I had no idea that I would be here today. I was a former football player. I didn't even know what blood products were. A company named National Medical Care, when I was trying to sell them some latex gloves, said, "We won't buy your gloves." I said, "What would you buy if we had

it?" They said, "We would buy some albumin." I said, "What is albumin?"

That is how we got into the business, and I have learned, and I was again struck by the comments here. I have learned, and our company has learned and maintained that same mission, to ask the customer. They have a lot of answers, and I think that is one thing that we are very good at.

After 11 years, we have nationwide distribution of especially pharmaceuticals, 80,000 square feet, 88 people, and I am very proud of the picture there, because we built that two years ago, but I also put this up for one reason. FFF houses the Federal Repository for Intramuscular Immune Globulin. We keep a reserve there that is not accessed unless we collaborate with the CDC, and there has been a shortage of IMIG over the last several years, and we have come up with some innovative situations to make sure that that product is available. So, that is the National Federal Repository for Intramuscular Immune Globulin.

[Slide.]

About our role in the marketplace, this year we will distribute close to 5 million grams of IVIG and 5 million equivalent units of albumin. We also administer some of the emergency allocation programs, the IDF Safety Net program, and the products that we distribute through the

IDF in collaboration with the IDF Safety Net program, the American Red Cross product, Baxter, Centeon, and we also do the emergency screening for Alpha Therapeutics emergency allocation program, so we have a lot of data, we have a lot of close contact with the physician and the patients.

[Slide.]

Those 5 million grams and 5 million equivalent units of albumin are distributed among the top 10 group purchasing organizations in the country. This is a list of the top 11. I think there is 9 bars that we have contracts with.

This is the market share that I think has been unprecedented in terms of a single company rising to, and it is not because we do anything better than anybody else, but we have listened to the needs of our customers, and we think we have responded accordingly.

[Slide.]

Our presentation is called A Premier Model. I wanted to emphasize the impact and the influence that a group purchasing organization has. Nearly every health care entity in the U.S. has some group purchasing affiliation, whether it be a hospital, a home care company, or a physician office, and when you combine those together, it is referred to as the latest acronym, the Integrated Health Network, but group purchasing organizations have a

tremendous amount of influence, and it is a tremendous amount of data that we can gather from that influence.

[Slide.]

When we bring on a new customer, a new contract customer, a new group purchasing organization, it presents to us a significant opportunity that we think has not been taken advantage of in the past. It is a data mining opportunity for us. We survey the demand for therapeutic plasma fractions.

We don't send out a survey and hope it gets mailed back. We exhaustively survey. We go out and ask the customer again what their needs are, what the demand is. We believe we have some of the most accurate usage data in the country.

We use that data to refine our contracting strategy, because for us to be successful, we have to meet the needs of our customers, and our customers are the hospitals, physician offices, home care companies, that are the members of the group purchasing organizations.

In a time of a shortage, a very labor-intensive effort that we put forth is what we call "interactive allocation system." Instead of putting a lot of product into a single location where one hospital may have 7,000 grams on hand, another hospital may have zero, we interactively allocate product to make sure that we are

meeting the moment of use demand.

Again, it is a very labor-intensive process, and i believe we are the only people in the country that do that. From that, from our sophisticated database systems, we monitor usage by GPO, by entity. You said this is what your demand was, you are over that demand, help us understand why.

We have got a new oncologist, we lost an oncologist, he has transferred to another facility, so we track usage by GPO, by entity.

Then, in the future--this may be considered a paid political announcement--but we have from talking to our customers, there is a need to track blood products to the end user. FFF has designed over the last two years a proprietary software product that can track blood products to the end user. It integrates easily with every hospital, home care, physician, or blood bank system.

It is very inexpensive, and it will provide for the first time we believe moment of use data. At the last Advisory Committee on Blood Safety that I was at, someone asked could we track product by patient, and to track patient movement when you have a shortage and you have an allocation, can you track that patient movement.

One of the characteristics of this last shortage--I feel like I am talking fast, because somebody said I only

had 15 minutes, and we are from California anyways, we talk fast out there--but someone said could you track, could you track the patient movement, and our Lot Track system will allow us to do that, because one of the characteristics of the last shortage that I believe has been dreadful is patients have had to migrate from provider to provider based on who had the product, and we would like to see an end come to that.

But the hallmark of the notification system is we can provide instant notification in the event of the first hint of product compromise. We believe anybody can distribute products. This distribution business is not a very exclusive club, believe me. I got in it. It is not a very exclusive club. [Laughter.]

Anybody can distribute product. It takes a company that really wants to help health care care get them back at the first moment of compromise, and that is really what our mission is. We are very good at tracking lot products. We endeavor to be the best in the world at it.

[Slide.]

I was reading the other day and I came across this quote. "To acquire knowledge, one must study, but to acquire wisdom, one must observe." Our observations over the past decade in this business have led to some of these, what we hope to be changes in the business.

One of my best buddies, who I think is one of the top guys in the fractionation business, this was a quote that he used, and when we present our program to group purchasing organizations, I always lead with this. The plasma fractionation market is characterized by steady, increasing demand met by inconsistent manufacturing. The risk of something happening is 100 percent.

I took his name off to protect the innocent.

[Slide.]

In thinking about the presentation, and when we talk to pharmacists around the country, over the last year, we have probably spoken to 1,000 pharmacists in settings just like this. This is probably the most important slide of our whole presentation because there is so little knowledge out there in the prescriber community as to the relationships between these products.

When I see this, I think of a three-legged stool, and in that three-legged stool, two of the legs are getting shorter. It creates a very unstable place to sit on. You have decreasing demand for albumin, you have decreasing demand for plasma-dried factor products, and you have got a burgeoning demand, unmet demand for IGIV. We have a very unstable situation here.

I believe we are at a crossroads here in this industry. Yogi Bear once said when you come to a Y in the

road, take it. I don't think that is what we are talking about here.

[Slide.]

I am not an expert is fractionation. I don't even want to say we are an expert in distribution. We are trying to learn it. But very simply put, the plasma manufacturing costs--and I didn't consult with anybody on these, I just picked what I thought would be the big ones--research and development, regulatory compliance, overhead, and yes, they do make a profit. People have to make a profit.

The reason that I think there is softness right now in the IVIG shortage is because the end user, the end user, the health care entity cannot make any money, and that is why there is a little bit of softness in the IVIG market right now.

It almost always comes down to economics, but if you think to the previous slide, I don't think these costs are coming down, first of all, and if they are, if somebody would correct it, I appreciate it. If these costs are coming down, manufacturers that do very well spread those costs over several different plasma fractions, hyperimmune globulins, the antihemophilic clotting facts, IGIV, and albumin is the one that I am really concerned about.

If the albumin prices go down or eliminated, or the plasma-dried factor products, I asked pharmacists what

do you think will happen to the rest of the products, and someone says, "I think they are going to go up," I always agree with them, I do, too.

[Slide.]

This is not an indictment of manufacturing business practices, I want to make that very clear. I have had the privilege the last month or so--and I think Dr. Goldsmith is in the room--to follow him in a few presentations, and I think when he presents his company's perspective on the fractionation business, I think he uses the number 210 days from the time of collection of plasma to maybe the finished goods lot release.

So, that is a long time. It's somebody else's math, but I think it is seven months. So, that's an awful long time. So, if we donated plasma today for fractionation, that product would be part of the new millennium.

But my point here is prior to that, when manufacturers finally get product released, they fulfill their contractual obligations to group purchasing organizations. If there is any left, they sell products to biological distributors at a higher price.

They deplete their inventory because it is a very capital-intensive business, and then they have very little or no reserve capability. Chris Lamb--I hope he is not in

here--the vice president of a plasma operation for the National Red Cross, in the April 12, 1998, pink sheet, said we have a three- or four-day supply on hand. It does not promote good patient safety and patient availability, and it is because it is a very capital-intensive business.

[Slide.]

I am going to go through this quickly and talk a little bit faster if I possibly could.

The traditional contracting model had been for a group purchasing organization to contract with one or two manufacturers, and invariably new manufacturer would have a better price. I am using albumin as a model here. You could plug in any product.

So, the health care entity, it may be a hospital, whoever has the best price, most of us would buy that because of health economics. So, the manufacturer who has the higher bid price may end up with some unrealized, not in the case of IVIG lately, but in the past has been true, may end up with some unrealized contract inventory, so the contractee would not buy their product, and then the manufacturer would sell it to a secondary distributor at a higher price, because they have to move the inventory.

What would happen is we would have maybe a manufacturing delay, a regulatory action, and whoever had been buying from their primary contractee in the past would

turn to the secondary awardee.

Then, what would happen is that product wouldn't be there because it has been sold to biological distributors. Then, the biological distributors turn around and sell it back to the hospital at a higher price.

It is probably the same product, but it turns around, coming back to them at a premium of 100 or 200, in some cases 400 percent.

We thought there is a better way.

[Slide.]

This is a bad word, and this is the things that I think have extracted a huge toll on our business. This bundling. This is not bundling that the manufacturers bundle. What this is, is a biological distributor will by product, IGIV and human serum albumin.

They will look at it as $114 for the investment in both products. Then, they will take that product to two different entities. They will sell IGIV, use $112. In the past, you could have plugged just about any number in there.

Then, they will sell the albumin for $45. On that $114 investment, they made $157, $43 profit, 27 percent. Somebody mentioned wholesalers, and somebody mentioned--I don't think anybody mentioned FFF, I think I did. Those are not the margins we work on. I wish they were, but they are not.

[Slide.]

Another example that is taking place now is something called swapping, that you don't hear a lot about. A hospital may have, because biological distributors will call hospitals, do you have any excess IVIG. Maybe they ordered some products for a patient, the patient got transferred, didn't show up, we have got 150 grams of IVIG. We paid $45 for it. The hospital's investment in it is $6750. The broker, out of the goodness of their heart, will say, well, we have some albumin, you may need some of that. We paid $54 for it. We will just swap it straight out, and we will take an apparent $1,300 loss.

They turn around, sell the 150 grams at $112 a gram to some unsuspecting other hospital or health care entity that absolutely has to have the product, and the original investment of $8100, that is a profit of $8700. This is stuff that I don't believe is good for health care.

[Slide.]

Because of that, we have tried to develop innovative situations and solutions to counteract some of those things. We are trying to provide, our company is trying to provide the most stable platform for the availability and affordability of plasma products.

Our primary, secondary program creates a primary level of pricing, as well as a secondary level of pricing,

at near as possible guarantee of availability, albumin pricing index, to make sure that all manufacturers that are participating in the contract have pulled through, we average our price, and we create an albumin price index, again providing stability to the pricing of the products.

Our interactive allocation system we talked about again and Lot Track. We believe the technology is here. We have successfully beta-tested the product at children's hospitals around the country, because we like to go where children are first, and the product works extremely well.

We have been using it internally now for a year, and it has cut our response time from the moment of withdrawal or recall to notification into seconds.

[Slide.]

The current market for IVIG. This is based on the observations we spoke about earlier. Nearly every institution in the country has implemented IVIG utilization guidelines. Those guidelines are usually a function of availability and affordability.

Right now I believe that the U.S. IVIG market, the demand has been suppressed while supply remains fairly constant. The demand is down. Our inventory build-up at FFF, it makes me chuckle because when I first spoke with Dr. Weinstein on the phone, he said, "How is the inventory level?" I said, "Hang on, I will go out back and look." I

said, "It looks pretty good right now."

We also monitor the spot market. There has been a dramatic decrease in spot market pricing. I think we can touch on that now.

[Slide.]

Here is how we view the marketplace. There is a primary contract rate. These are averages, we didn't put up exact numbers, but the primary contract rate in the U.S. has risen to about $39 per gram. Somebody was asking about Europe. There is a preponderance of companies trying to get product into the U.S. It is for one reason - higher average selling price. It is very simple. I always believed--I would like to believe that they were coming in here to address the human situation. I think it is to get the highest ASP humanly possible.

The secondary contract, as part of our primary secondary program, it is hovering around $50. The emergency allocation programs that have provided great relief and I think a great sense of security for a lot of patients and practitioners in the U.S., and have a tremendous amount of value, range between $50 and $65.

The spot market is $70 approximately right now, but you hear outliers, the highest that I had heard over the last 12 months is $300 per gram. That is--I don't want to say what I think it is.

[Slide.]

Responding to Mark's question, how is the inventory build-up at FFF, we trend these on a daily basis. We believe the group purchasing organizations hire us to manage us the blood products market. It is a dynamic, it's a fast-moving market, and it changes. It changes on a moment's notice.

So, we have been trending here, and on a linear trend, the blue line is sales, the green line is our inventory, and we see a widening in-between our sales and our inventory, we are having an inventory build-up. This is temporary. The availability today in the U.S. of IVIG is better than it has been in the past six months. We believe it is temporary, and it is because of those utilization guidelines.

Those utilization guidelines are in place, and I will address those a little bit more later.

[Slide.]

We talked about our data mining opportunity. We have surveyed 3,079 of the 6,056 hospitals in the U.S. Again, it is not a mail-out survey. It is talking to the practitioners, it is talking to the pharmacists who are the gatekeepers, and I think we have a pharmacist who is going to come on later, but those are the gatekeepers of the product.

From our extrapolation on the ones we did not survey yet, we believe the demand in the U.S. for albumin is 11,482,000 equivalent units. The albumin market is not operating at that level right now. It is falling far short of that. It is because of the utilization guidelines that have been in place. There is an economic reason for that.

[Slide.]

I think the IGIV numbers, which probably this crowd is more interested in, was 18 1/2 million grams. I was thinking back as I was listening to the first conversation before I got here, I was thinking back. In the last two weeks I have sat with executives from the plasma fractionation market, one said the demand is 21 million, the one said it was 25 million. So, we don't actually know.

I am not saying we know either, but we are asking our customers.

[Slide.]

I think the good news is that there is a change in business practices that are taking place because of some of the toll that has been extracted on the health care community by the biological distributors. There is a change in business practices, and it is for the positive.

Alpha has a direct contract only, not selling to biological distributors only. Baxter is doing exactly the same thing. Bayer has implemented a sales price cap, so

those excesses, those are very positive moves. For the first time, we are seeing those take place, and we support that, and Novartis has a semi-closed distribution system. I look at that as very positive.

[Slide.]

If we could be so bold to make some recommendation. We believe that through GPOs and our Premier Model, there is an opportunity to communicate supply information to the practitioners.

There are two types of shortages, I believe. There is a shortage when you absolutely cannot get the product and it is not available. That is definitely a shortage. Then, there is a shortage that I think we are in right now where patients are not aware of availability and are being denied care.

To us as a distributor, that one is a little bit more simple. If you don't have the product, that is certainly understandable, but if it is there and it is not a responsible distribution channel, those are the things we have to change, and the utilization guidelines must be dynamic to protect all patients. Typically, they are not.

We layer over a utilization guideline, and I refer to it as "shutting the faucet off." We tell all practitioners it is just not available. Someone was talking about off-label demand right before I came up, and for those

folks, the faucet has been turned off.

There is no mechanism in the U.S. heretofore where you can turn the faucet back on, and prescribing patterns often continue to follow the last set of guidelines, and I believe again there is an opportunity here to mandate the tracking of blood products to the end user.

You will increase the safety of blood products, and it will also remove the mystery from supply and demand, because when you have an industry where the middlemen or the distributors make more than the major stakeholders, the manufacturers in some cases, then, that is characterizing the biological distribution market, it is characterizing the home care, you have a problem, and we are seeking to change that.

[Slide.]

Our marketing strategy is listening to the needs of the customer, and I appreciate your time listening to us.

Thank you very much.

DR. HOLLINGER: Thank you.

The next speaker is Allen Dunehew, Director of Managed Care Contracting and Fractionated Blood Products, Premier Purchasing Partners.

Allen R. Dunehew, R.Ph., M.P.A.

[Slide.]

MR. DUNEHEW: I work with Premier Purchasing

Partners. We have several offices across the country including one office in Washington here. Our primary job is to advocate for our members. I will show you some slides to give you an idea of the impact of Premier throughout the health care industry in the country.

We are wholly-owned by our members. We have about 220 shareholders. So, our total focus is really to meet their needs and to advocate for them, and to work for them.

[Slide.]

This will give you an indication of our penetration into the country, and I have another graphical of high demonstration that gives you a better idea, too, but we are really well represented throughout the continuum of care, which is an important issue certainly as we talk about these products, blood products.

We have worked with FFF to put together what we think is a fairly unique program and is working well for our members today in a very tight market, although that changes daily, as you know.

Again, roughly about one-third of the health care in the country belongs to Premier.

[Slide.]

This is just to show you the different types of organizations. We have both small rural hospitals, as well as medical centers that belong to us, individual and

physician group practices, hospitals, home health, home infusion, as well as HMOs.

[Slide.]

This represents in the GPO world, group purchasing organization world, our penetration into the market. Again, it is about roughly one-third. On any given day, some of these numbers change based upon who robbed the last member from them and joined their group.

[Slide.]

To give you just a little bit of a background on the history of this program and why we put it together. We started on this probably about a year and a half ago, and as you know, at that time, albumin was still a little bit of a problem, but IVIG was beginning to be a significant problem, and certainly it has gotten worse since then, and we had a serious issue with the way the program worked before under the contracts.

We had only three manufacturers under contract through manufacturers or suppliers, if you will, and we felt that there was a need really to significantly increase that, and the availability of product, so we extended that out to essentially all of the manufacturers or suppliers within the country.

One of the problems we had before was that the distribution channel and the selection distributors was

actually designated by the manufacturer, and so the problem that created for us, particularly in a tight market was because of a chargeback system, and if you really want some information on distribution, I can give you that at another time or off line, but there were some incentives in the distribution system, in the standard distribution system in this country, and they still exist today, although not in our program, because of a practice called chargeback mechanism, whereby an item would be purchased at a list price, if you will, and when it was sold under contract it would be sold at a lower price, and that distributor or wholesaler would go back and charge back to the manufacturer the difference between the contract price and the selling price.

If that distributor chose not to sell it under contract, but to sell it to anybody else, they could do that freely. They were allowed to do that. So, we did not have control over the product to make sure that what we had under contract actually went to our members.

Really, Novartis worked with us in the very beginning of putting this together, and actually pushed us to start the program a little bit before we were ready, because they realized the same issue because the majority of their product was distributed through the typical pharmacy wholesaler under the chargeback mechanism.

Today, we have one distributor, and we had RFQs from I believe it was eight or nine specialty products distributors across the country, and based upon what Patrick and his organization could offer to us, we made the award to them for an exclusive agreement.

Today, we have complete audit capability on the total product that is supposed to go to Premier members. I know monthly how much is supposed to come in to the program, and I know every sale that occurs to our members, and I total that up and check that every month to make sure it only goes to our members because that is what we are doing, we are advocating for them. It is very important.

Even with that, we still have not been able to get enough, certainly enough IVIG to meet their needs.

Another thing that we did was the last bullet point on that last slide, which I think is important, and we treated all members as equals. I can tell you when we set this program up July 1st, I had hundreds of calls a day from our facilities complaining because it was a significant change in the way they do business.

Again, I am not trying to slam manufacturers, I wouldn't do that because they are important business partners for us, but their alignment of goals and decisions are different based upon how they do things and which facility, which hospital, or home infusion company might

give more product because they are looking at it as how it relates to the total product line that that facility buys from them.

I can remember one comment from a teaching facility, and they said, you know, "We should IVIG because our patients are more important," and my response back to them was, "Well, you know, if I had a child and I lived in a rural area, and they were treated at a 45-bed medical center, and they needed IVIG, I would have a hard time believing your stance on that."

So, what we tried to do is really put this uniformity in the system and accountability on all partners.

[Slide.]

You have wanted some numbers, so we have got some numbers for you, and these are facts, and we track this monthly.

DR. HOLLINGER: Mr. Dunehew, I am sorry. I have seen equivalent units. You have used it several times. Just tell me what that is.

MR. DUNEHEW: Equivalent units on albumin is a 12.5 gram equivalent unit. That is the way we measure it.

DR. HOLLINGER: 12.5 grams?

MR. DUNEHEW: 12.5 gram equivalent unit, right. We don't use equivalent units on IVIG. We use grams because it is easier to follow.

We did a survey back in January of 98, so this data really is supported by two surveys of our members and again of about 1700 or 1800 facilities. In January, we came up with about 3.2 million grams, and that was a very small return on that. We were very dissatisfied particularly when you look at the problems in the market at that time, but actually when we put the program together in June of '98 and FFF assisted us and actually went out and talked to all of our facilities in setting up our allocation program, that was confirmed that really these numbers were accurate.

So, albumin and IVIG were both at a demand of about 3.2 million units and grams respectively, and not much has been mentioned about albumin today, because I realize that is not a shortage issue, but I have to tell you I am a little bit concerned about our ability to continue to get IVIG because albumin has become a soft market and that is a factor that I think really needs to be considered, as well.

So, in spite of that 3.2 million amount that we needed, with albumin we are okay, we were able to get everything we needed and actually we had a little bit of excess, but when you look over here at IVIG, we could only get 1.8 million grams, and that was a significant decrease from what we had had in the previous year, in '96 and early '97, for that matter.

So, we had really a shortfall of about 1.2 million

grams. Shortly after we went into this in July, as you know, one of the manufacturers that we were depending on stopped shipping product, but our other manufacturers were actually very good to us and stepped up to the plate and really supported the program, and we were actually able to make up for that difference and get a little bit more here, so we were able to get about 2 million grams over this past year.

Now, we are very happy about this. Through a lot of finagling and discussions and different angles, we were able to increase the amount of IVIG. The next slide will tell you some of the reasons why we were able to do that, but we still have an unmet need of about 0.3 million grams, but if you look here, we have only got about 2.1 million of albumin under agreement now, it is actually a little bit higher than that.

That is at our request because the albumin need has decreased so significantly, and as a practicing pharmacist, I get pressure sometimes to try to promote the use of albumin, but I can tell you, if you can use an 80-cent liter bag of saline instead of albumin, that is a good move if the patient outcome is the same.

I would stress that when you try to look at those decisions, as well as it relates to off-label use of IVIG, that doesn't necessarily mean that is bad. Really, what

should be considered is what effect does that have on the patient in terms of outcome, is there an improved outcome from the use of that product, and if it is, it is appropriate even though it might be off-label.

But in fact, there are a number of protocols out there, and we have them in our own institutions where they say you cannot use it for off-label use if our supply stock falls below a certain safety level, like 200 grams on the shelf, and those are out there and in place today.

[Slide.]

Reasons for the two-year increase. I don't want to make you think that the shortage of IVIG is over because I don't think it is. I think that there is still certainly a need for more, and anything that can be done to increase that supply is very important.

It is also very important because as you well know, the supply status of a given company from day to day or week to week, as we experienced a couple of weeks ago or a week ago, changes overnight, and it can dramatically change the market. So, I think the effort should really be to increase the supply.

Again, some amount of production increases from our contract with manufacturers, negotiations with the business partners, substantial price increases. We have had substantial price increases. One company that I won't name

has increased prices from the price we had in '98, before the program, about 100 percent going into the first year, and we just experienced about another 30 percent increase, so price increases are out there, and they are happening, and I could talk with you more about that later.

And then the success of the dedicated distribution program, and I think the manufacturers today understand that this has worked well for them, as well.

[Slide.]

Measurement of availability. Just some suggestions from my perspective that I think would be of some assistance. That is, groups, such as Premier could be used as a reference on a monthly or quarterly basis. What are we receiving into the program, and what is being ordered, is there any excess supply, you know, even to the point where if there was a need for a survey, perhaps there could be some assistance put together for that.

I think this is a good measure. IVIG, if you are looking at it, just monitor the spot market price. If it is $130 a gram, you know, there is a significant shortage because they are able to sell it at that price. Spot marketers, sometimes I refer to them as privateers or pirateers I guess.

The other part of it, too, is if it gets down to $50 or $60 a gram, supply is pretty good. You can get it

for most needs. Availability of product under the Emergency Supply programs--and this changes, too, based upon availability--and then there maybe is an opportunity for an FDA web site through something you already have created, that is specific to this issue, and we could even help publicize that with our members and get that information out that if there are supply problems on a patient level basis or whatever, then, we could help get that information.

[Slide.]

Some general suggestions. Communicate supply status to physicians or changes in supply status to physicians and health care practitioners. I think this is important, if, in fact, the IVIG market does soften up a little bit, because those facilities that have protocols in place, probably need to decrease the enforcement of those protocols, and we try to keep our members up to date on where we are.

Recommend flexibility in the application protocols. Continue to work to increase the overall supply, as I mentioned before. I do think that that is important. Again, I am concerned about albumin, because it is going to have an impact. I am not sure what it is, but it is going to have an impact on IVIG availability one way or the other, and again, the off-label use is not necessarily bad use, it is what impact does it have on the patient outcome for that

indication.

Thank you.

DR. HOLLINGER: Thank you.

We have got two more discussants and someone who has asked to speak in the open public hearing plus anything that anyone wants to say. What I would like to do is maybe just take a 15-minute break.

It is 4:33, so let's say around quarter until 5:00 we will break.

[Recess.]

DR. HOLLINGER: We will go on here.

I think this is also a critical discussion, is demand being met. This is important because now we are going to have a perspective from the user community, and the first speaker will be Mr. Patrick Collins from the National Hemophilia Foundation.

Is Demand Being Met?

Patrick Collins

MR. COLLINS: Thank you, Dr. Hollinger, and good afternoon, everybody, or should I say good evening by now.

My name is Patrick Collins and I am Director of Government Relations at the National Hemophilia Foundation. Presenting with me will be Thomas Moran, President of the Immune Deficiency Foundation.

We would like to discuss the current demand for

product and whether or not that demand is being met. I will speak about the current demand for clotting factors, immune globulins, and alpha-1 proteinase inhibitors. Tom will then discuss the greater concerns and demands for plasma derivatives as a whole and conclude with some suggestions on what the plasma manufacturers, public health service, and consumer groups can do to remedy the supply and demand issue.

I think clearly today we have seen a difference between those who are experts in the field of methodology and those who are experts in the field of disease, and I hope that after our presentation today, that difference will be cemented.

I would like to start with the most glaring example of a product that is in great demand, yet is not anywhere close to having that demand met. Individuals with alpha-1 antitrypsin deficiency depend on the alpha-1 proteinase inhibitor to prevent lung damage from infections that cause the loss of lung function, disability, and ultimately death.

The demand for this product is great, yet there is only one available licensed product within the United States, that being Prolastin by Bayer. Unfortunately, Prolastin is being rationed at 50 percent of historic purchasing levels for distributors and care providers.

There are approximately 5,000 individuals who realize that they are antitrypsin deficient in the United States, and they cannot get product. These 5,000 individuals are basically held at the whim of the Bayer Corporation.

A unilateral reduction of product by 50 percent has made this community the most glaring example of individuals who are in desperate need of product, yet, they cannot get it. Obviously, Bayer has not met the demand for this product in the antitrypsin deficient community.

Regretfully, the Alpha I Foundation states that this situation will in all likelihood continue until two other products, which are in Phase III trials currently, are licensed are leased onto the market.

What is a community to do when this demand for product is not met? Comes before this advisory committee, as well as others, time and again. Let's hope that one day the demand for alpha-1 proteinase inhibitor is met, because right now it is not, and unfortunately, people's lives are at stake.

I would now like to take a couple of minutes to review whether demands for coagulation factors VIII and IX, inhibitor products and von Willebrand factor have been met.

With regard to factor VIII, NHF has appeared before both this committee and the Blood Safety and

Availability Committee to discuss the shortage of factor VIII, specifically, recombinant factor VIII.

The situation was rather dire at one point until October 1998 when Baxter Health Care received FDA licensure of their recombinant plant in Thousand Oaks, California. Baxter's product release has helped to significantly ease the shortage. Supply data that the IPPIA makes available indicate that the distribution of factor VIII, specifically recombinant, has begun to increase as a result of this influx of product.

For the last available month in the IPPIA supply data, at least the data that I receive, March 1999, over 103,000 international units of recombinant factor VIII were in inventory. This is the largest inventory in almost one year.

In our informal polling of the hemophilia treatment centers, there is some difficulty in having supply met based on which manufacturer the center may have a contract with, but product now does seem to be available. Some work and creativity may be required to obtain this product, but it can be obtained.

I would just like to comment briefly on an overhead that Mark Weinstein had on the overhead about an hour or so ago with regard to the distribution of factor VIII. Mark claims that the distribution has been pretty

constant, and I wouldn't necessarily disagree with him, however, I think it is incontrovertible to argue that both Bayer and Baxter at one point were on allocation.

So, while factor VIII distribution may have been more or less constant, recombinant factor VIII, of which approximately 70 percent of the population was on, that distribution was not constant.

As a result of that, people had to switch in some cases, and quite a few cases, to high purity plasma-derived product, and the IPPIA data does reflect that for the summer months of 1998 specifically. Some had to switch to medium purity product, basically, any product they could get from all the way down to Joe's backyard sludge factor plant, but while the distribution may be constant, the quality of that product was nowhere near constant.

The hemophilia treatment center polling that we did does indicate an underlying concern. Although recombinant factor VIII is obtainable, it is not readily available. As a result of the HTCs report--and this is informal data, basically me getting on a phone calling every HTC--but they state that while getting product in some cases was difficult, but they were more or less able to get it, that some treatments, such as elective surgeries on numerous occasions, as well as immune tolerance and prophylaxis treatment was deferred.

These procedures are treatments are part of the demand that the bleeding disorders community has for product. Surgeries, such as joint replacement, while classified as elective, are a major need for many individuals who have to deal with chronic pain as a result of hemophilic joint destruction.

Moreover, immune tolerance treatment is a universally recognized method to eliminate inhibitors, and prophylaxis is recognized as a good method to prevent bleeding disorders. By having this treatment deferred, a person, in most cases a child, does risk life-threatening bleeding episodes.

Having access to immune tolerance treatment, prophylaxis treatment, and elective surgery is one desire, in fact, it is a demand, of the bleeding disorders community. Unfortunately, there is not enough available product to meet this demand.

Factor IX deficient patients are in a far worse situation, unfortunately. While the recombinant factor IX benefits is readily available, there is a percentage of the community that either cannot afford the product or have had a negative reaction when using the product. Hence, these individuals are relying on plasma-derived factor IX products.

Unfortunately, the plasma-derived products are in

incredibly short supply, factor IX specifically. The IPPIA supply data states that for March 1999, only 3478 international units were in inventory. In our informal polling of the HTCs, more than half of those responded cited difficulty in acquiring plasma-derived factor IX product even for routine use. I think that is an obvious case of demand not being met.

The same holds true for inhibitor bypassing products. The HTCs overwhelmingly reported difficulty in acquiring such products.

Lastly, for von Willebrand factor products, there is just presently not enough data to judge. Many factor products are use off label in treating bleeding episodes in von Willebrand patients, and just recently the FDA for this indication approved human AP. Yet, the availability of this product, as well as other factor VIII concentrates that have been successfully used to treat von Willebrand disease have been dangerously limited.

Will the licensing of human AP ease the situation? We can only hope so.

The bleeding disorder community views as necessary having enough product, so that a normal life can be lived without the fear of a bleeding episode, having enough product available for elective surgeries, such as joint replacement, and having enough product available for

preventive treatment, such as the elimination of inhibitors and prophylaxis treatment.

These are the needs of the bleeding disorder community, and they are currently not being met.

Lastly, with regard to immune globulin, I think it is fair to say that we are aware that demand for this product is not being met. The Shays Committee had a hearing last summer, which I am sure we are all well aware of, as well as 60 Minutes, which profiled the situation in detail last summer.

In 1996, 17,000 kilograms of IGIV were consumed in the U.S. marketplace. In 1998, 15,200 kilograms were released to the U.S. market, which is a reduction of over 10 percent from the 1996 levels.

Projecting IPPIA data on IGIV released through April 1999, it appears that 1999 IGIV levels will be very close to those in 1998. In prior BPAC meetings, the Immune Deficiency Foundation has reported on the significant negative health consequences of the IVIG shortage to its members during 1998.

I would like to now turn it over to Tom Moran, who will speak in more detail on IGIV specifically, as well as discussing action steps required for industry and regulators in light of this dynamic situation.

Thank you.

Thomas L. Moran

MR. MORAN: I have got about a five-minute presentation, Mr. Chairman, so I will get through quickly.

[Slide.]

I just wanted to comment on an earlier point that was raised related to someone asked a question about the FDA's--since the last BPAC meeting--the FDA's efforts with respect to licensing new products and the issues of surrogate markers, and so forth.

Dr. Golding responded on behalf of FDA, and I just wanted to add my confirmation that IDF is working with three companies now with the cooperation and the assistance of FDA, and I think there is progress being made with respect to moving some product approvals through the system, and I think that perhaps by the next BPAC meeting, there may well be some very tangible evidence of that.

As Patrick Collins has just pointed out, there are serious personal consequences when patients are unable to obtain or afford their therapies. The testimony at previous BPAC meetings of the Alpha I Foundation and the Immune Deficiency Foundation, and others, have reported serious adverse health consequences within our communities resulting from shortages of plasma derivatives.

It might be useful to revisit one piece of data from the IDF Physician Surveys conducted in April and August

of 1998. This data captures how physicians and the pharmacists who order for them adjust to market shortages and how this might affect personal health.

[Slide.]

Many of the strategies listed on this chart result in a reduced use of IGIV. One could call it reduced demand. For example, when physicians postpone scheduled infusions, switch to different IGIV brands, increase the interval between infusions, reduce the dosage, or eliminate therapy altogether.

Basically, what happens is you have a diminished demand for a short period of time, but this raises questions about the quality of health care that the patients are receiving.

[Slide.]

In response to the IVIG shortage and in response to the health care related problems our patients were having, the IDF, in cooperation with the IGIV brandowners, listed here, and FFF Enterprises, established the Safety Net program to provide IGIV on an emergency basis to physicians, stipulating a need for product based on medical necessity.

[Slide.]

To date, 368 physicians have enrolled in this program, 132 immunologists, 236 physicians from other specialties.

[Slide.]

Between January 1, when the program began, and May 31st of 1999, 76,000 grams of IGIV have been shipped at the request of IDF through the Safety Net program.

[Slide.]

1,224 patients in 43 states have benefitted from Safety Net.

[Slide.]

Sixty-eight percent of those patients, or 826, have diagnoses of primary immunodeficiency disease. I would just like to point out very quickly that IDF does not limit the distribution of IVIG to primary immunodeficient patients, but rather distributes it based on the representation from physicians of medical necessity, and this is an issue that was discussed earlier.

A comment that I have made in previous meetings is that on-label and off-label is not necessarily the same discussion as medically necessary or non-medically necessary.

[Slide.]

We have trends although we are dealing with a much smaller quantity of product than Patrick discussed earlier, and as you can see, these are three of the products that we distribute through Safety Net, and what these graphs represent are really a velocity or product moving into the

IDF Safety Net program and off, so the data points are how quickly that product is exhausted.

As you can see, the trend from March through May in all three products was slightly up. I will say, however, that we, too, have noticed in the last several weeks a subtle softening, if you want to call it that, and perhaps if we had June data, it may show a similar kind of down trend to what Patrick has shown.

However, I think another explanation for the apparent discrepancy between the FFF data and the Safety Net trend lies in the fact that we are seeking out spot shortages as distinct from the spot market.

We are seeking out places that cannot get IGIV that might be outside of the general purchasing organizations, and these kinds of spot shortages come to our attention, so that may help explain the trend if, in fact, there is a softening in the general market.

I would, however, caution FDA and the committee to avoid over-interpretation of short-term trends in a market where we know we are still 10 percent below historical supply levels.

This leads me to the main point that plasma consumers would like to make. Well, just one other comment before I make the main point.

[Slide.]

The IGIV supply in the United States, April 30th of 1999, as estimated by IPPIA at 10 days in '98, 11 days, so I am not quite as sanguine as some of the other presenters today about the shortage may be over.

One can imagine any number of scenarios including a strike by UPS, for example, that could well--10 days is not a big safety margin.

[Slide.]

The point, however, that we want to make is that as product shortages persist, the market adjusts to the current supply reality, a kind of equilibrium occurs, and what happens in the marketplace are things like the rationing protocols that Allen Dunehew mentioned, where hospitals are in effect rationing IGIV.

Alternative therapies are employed where possible, maybe not equivalent therapies, but alternative therapies. Some therapy, as we saw in the first slide, can be eliminated. Patients migrate to different sites. If they can't get it from their home care company, they may well get it from the hospital.

[Slide.]

As a result of these adjustments to supply, the public health consequences of these adjustments must be understood in order to develop appropriate public policy responses. The question of the current theoretical upper

limits of demand is an interesting question and probably important to corporate planning for investment purposes, but the more relevant question for consumer groups, and we believe for agencies mandated with public health responsibilities, like FDA and CDC, is what are the health consequences to patients of different levels of product supply.

What I am suggesting is we may be stuck at a situation where demand equals supply at 15 million grams, for example, of IGIV, where people are being undertreated or not being treated, and there may, in fact, if pharmacists and physicians and others get used to this availability, this level of supply, we can have a persistent situation where less than optimum health care is being delivered.

[Slide.]

Expressed differently, in markets like IGIV, A1PI, and certain clotting factors, where there is 100 percent consumption of existing product, are we failing to meet the therapeutic needs of patients with accompanying adverse health consequences?

I would like to assert that in my opinion this is probably the case today. What the consumer organizations are recommending, and following on to I think what was implicit in a lot of the presentations today, is that I think we need to find out what the facts are.

[Slide.]

I guess the difference in our perspective is we would take it from a health point of view rather than a supply and demand point of view, but I think a collaborative effort that involved consumer groups, medical societies, pharmacists, distributors, general purchasing organizations, manufacturers, U.S. Public Health entities like FDA and CDC, I think we need to get together and find out are we stuck in second gear and are people getting sick as a result of that, or are the consequences of the shortage from a public health perspective not quite as significant as perhaps we believe.

[Slide.]

The kind of data that we look at is how are these products used by diagnosis. If you take IGIV as an example how much of the product is being used on-label, off-label, how much is being used in medically necessary areas, maybe how much of it is reaching areas that are generally agreed not to be medically necessary.

How are products, for example, like clotting factors being used with respect to prophylactic treatments versus acute care, is there product enough to provide prophylaxis. Stage of disease that these products are being used at in the A1PI community, the Alpha I Antitrypsin community, is it simply people that are in late stages of disease, or is there enough product to get patients in early

stages of disease on product.

Finally, are patients having to migrate from one treatment setting to another in order to get their drug.

The distinction we are making is between levels of care based on emergency supply versus optimal care based on accepted medical standards. We think that the discussion and research, data collection, data analysis needs to take into account the health consequences at each level of supply, at each level of these products.

I don't think this has to be an extraordinarily complex undertaking although I know it is not easy. I think FDA notice could well get a lot of cooperation from all elements of the industry including the consumer group to accomplish this, and I think that is where we need to go.

Thanks.

DR. HOLLINGER: Thank you.

Any questions for these last two speakers?

[No response.]

DR. HOLLINGER: If not, one person asked to speak in the open public hearings, and that is Nancy Buelow, who represents Alpha I National Association.

Open Public Hearing

MS. BUELOW: Good afternoon. My name is Nancy Buelow and I am here today to represent the Alpha I National Association.

We have only one manufacturer, and that manufacturer cannot meet demand for the people who have alpha-1 antitrypsin deficiency. We are currently under a 60 percent allocation based on patient population that was in 1997. We are diagnosing a new alpha every day, and they can't be treated because of lack of product.

We have patients of long standing that suddenly have no product at all. Unfortunately, this usually starts in the VA, and a lot of these are Viet Nam veterans.

I am one of those people that you have referred to today, the other people, and we live in constant fear, wondering when we will get our next product, where it is going to come from, and if we are going to have it.

Without product, we are very vulnerable to lung infections. When we get a lung infection, we can lose quite a bit of lung function at a very fast rate. I am just recovering from a lung infection. I have 36 percent lung function, which I can do pretty well with, and I would like to keep it.

We are hearing that full production will not ever meet our demand. We need more product and a safe product for this life-sustaining drug. I would like to thank you for the supply and demand continued discussions. I would also like to thank Mr. Collins and Mr. Moran for their perspective.

Our community needs to know what can be done to help us, and, please, ask the industry to address when we can expect to again get our full prescription dosage at our weekly intervals.

Thanks for the opportunity to address these concerns and holding this committee.

DR. HOLLINGER: Thank you.

Anyone else from the public wish to make a statement?

[No response.]

Committee Discussion

DR. HOLLINGER: If not, we will close that portion and then just see if there is any issues that should be dealt with here by the committee. A lot of this was information about where I think we stand at the present time with many of the products.

Is there anyone that has any issues that they would like to discuss? Yes, Dr. Ohene-Frempong.

DR. OHENE-FREMPONG: I have a question about the alpha-1 proteinase inhibitor production. Is there anybody here representing--is it Bayer? Is there any reason that anybody can give for why there are only 50, 60 percent of demand? Is this something very difficult to produce?

MS. HUXSOLL: My name is Jean Huxsoll, and I am from Bayer. It is not a decrease in production. It has

been an increase in demand. We recognize that if the increase in demand continued, there would be a shortage as there was with IGIV, so the 60 percent limitation was set so that we would not end up with some consumers not having any product at all.

DR. HOLLINGER: I am sorry. So, product was mostly a decision made to produce Prolastin as well as well as IGIV, is that what you are saying?

MS. HUXSOLL: No. The Prolastin production has not changed. The demand has increased. So, in order not to have a shortage the same as we did about a year ago with the IGIV, the 60 percent limitation was put on, so that there would be product available.

DR. HOLLINGER: Why do you think the demand has changed?

MS. HUXSOLL: I am sorry, I can't answer that. I don't know.

DR. KOERPER: I think there is more people being diagnosed with this.

DR. HOLLINGER: Anyone else? Yes, please.

DR. MITCHELL: How long do you expect that the demand will stay at high levels, and are you planning on being able to meet those demands?

MS. HUXSOLL: I can't answer the question about the demand, but I can tell you that one of the things that

we are trying to do right now, the product has a very low yield and comes from an intermediate fractionation product. We are presently processing all of that material that we have in house, but we are looking at establishing contracts with the other manufacturers, so we can buy that intermediate from them and increase the production.

DR. MITCHELL: Do you have a time frame on that?

MS. HUXSOLL: I know that a present contract is being negotiated as we speak, and we expect to get material in the next month or two.

DR. HOLLINGER: Are there other manufacturers of this product?

DR. EPSTEIN: There are IND holders.

DR. HOLLINGER: Yes, please.

MS. MARA: My name is Judy Mara and I am President of the Alpha I Association. I just wanted to clarify a little bit. Even though we are on 60 percent allocation, because of distribution inequities, we have many people not getting product at all, so that that is a real big problem for us.

Also, anyone newly diagnosed for the last year has not been able to get product.

DR. EPSTEIN: I just wanted to ask Judy Mara, could you just state for purpose of clarity whether Bayer is at full production in all its facilities or not? The

previous speaker I am asking. I am sorry, Jean Huxsoll. I am sorry, I asked the wrong person, my fault.

MS. HUXSOLL: Yes, it is my understanding that we are at full production.

DR. HOLLINGER: That is the only manufacturer of that product available, is that correct?

DR. EPSTEIN: Again, there are some IND products, but there is only one licensed product.

DR. HOLLINGER: One licensed product at the present time, some in IND. Okay.

Dr. Boyle.

DR. BOYLE: I would just like to point out that we have been in the IVIG shortage for some time, and I am encouraged today because we have learned some new things that we didn't know a year ago, but we are faced at this committee with a lot of decisions and a lot of decisions we have to make with fairly limited information.

Now, one of the things we learned today was the 10 percent estimate about demand turns out to be based on qualitative research. I don't blame the people who do the qualitative research. I have done the focus groups and seen the people in the back room say three of the people like my product, that is a 30 percent market share, but it is very important to recognize that that data really doesn't tell us what we need to know.

It is also important to note that because the FDA at least currently does not produce and distribute gamma globulin, the likelihood that continued calls to them will represent the unmet demand, it just isn't going to happen. If they call and you can't help them, they are not going to call you back.

What is very important for us to understand in the future is to get true measures of demand. I think it is important that some of the things that were suggested sort of towards the end, that there needs to be some improved information collection and that because of the different parties involved, government, industry, and consumer groups, there has to be some effort made to try to bring them together to get that better information.

DR. HOLLINGER: I was impressed with listening to some of the presentations today, at least that the distribution seems to be getting in hand a little bit, so you don't have these areas where there is no product and some product at least, as well as a control on the cost, which seems to be was a critical problem at one point of who could get it, and then if that person could get it, how much it costs.

That, at least in the marketplace, seems to be working toward smoothing that out a little bit, and I think that was very encouraging over the past few months.

Anybody else with a comment?

[No response.]

DR. HOLLINGER: I appreciate everybody's responses today and discussion. We will start tomorrow morning at 8 o'clock.

[Whereupon, at 5:20 p.m., the proceedings were recessed, to resume at 8:00 a.m., Friday, June 18, 1999.]

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CERTIFICATE

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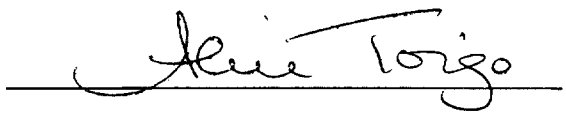

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