PUBLIC HEALTH 2000: IMMUNE GLOBULIN SHORTAGES—CAUSES AND CURES

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RESOURCES

OF THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

HOUSE OF REPRESENTATIVES

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PUBLIC HEALTH 2000: IMMUNE GLOBULIN SHORTAGES—CAUSES AND CURES

THURSDAY, MAY 7, 1998

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RESOURCES,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:35 a.m., in room 2154, Rayburn House Office Building, Hon. Christopher Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Snowbarger, Pappas, Towns, and Kucinich.

Staff present: Lawrence J. Halloran, staff director and counsel; Anne Marie Finley and Marcia Sayer, professional staff members; Jesse S. Bushman, clerk; and Cherri Branson, minority counsel.

Mr. SHAYS [presiding]. I'd like to call this hearing to order. We welcome our witnesses. We welcome our guests.

Persistent shortages of a critical medicine are endangering the lives of patients and threatening the public health. Inadequate supplies of immune globulins, IG, disease-fighting antibodies extracted from blood plasma, pose a profound challenge to the entire health care delivery system, forcing patients, their physicians, drugmakers, and regulators to confront the excruciating realities of scarcity and rationing.

The health of many thousands is at stake. More than 50,000 Americans suffering immune deficiencies must have regular access to intravenous [IV] treatments to avoid deadly infections. Today, they face the unhealthy prospect of delayed IG therapy, reduced dosages, price gouging, or no treatment at all. Public health officials need quick access to adequate supplies of intramuscular [IM] immune globulins to meet disease outbreaks, as in 1997, when hundreds of school children were exposed to Hepatitis A from contaminated strawberries. If that outbreak occurred today, there would not be enough medicine to treat the victims.

What is causing the shortages? Plasma fractionation companies and the FDA point to three factors: one, increased demand; two, decreased production, and, three, decreased availability of finished products after withdrawals and recalls to address the risk of transmitting Creutzfeldt-Jakob Disease [CJD].

Exports also reduce the amount of IG available to patients here. Blood and plasma donors provide a precious community resource with the expectation it will benefit their neighbors and countrymen, particularly in times of shortages. Yet exports of IG from U.S. plasma held constant in 1997 at more than 20 percent of total pro-

duction, even as domestic supplies fell by 10 percent and even as Europe was suffering no shortages. That is very troubling to many patients and an issue that must be addressed by the manufacturers, regulators, and perhaps by Congress.

FDA estimates there was a 20 percent shortage of intravenous IG last year. The IG exported by major U.S. fractionators in 1997 would have met more than three-quarters of that shortfall. A major portion of that shortage can also be attributed to reduced production, particularly on the part of one fractionator, Centeon, which closed a plant while bringing the facility into compliance with regulatory safety standards. Precautionary measures against CJD suppressed overall supply by less than 5 percent.

Demand growth and other factors accounted for the remaining deficit. Demand for intravenous IG continues to grow about 10 percent each year, fueled primarily by off-label uses. These are IG treatments prescribed by physicians but not fully tested for efficacy or appropriate dosage levels. The full extent of off-label use is not known, but may consume as much as 70 percent of total IG production. Efforts to curtail off-label usage during the shortage appear ineffective.

This hearing will explore the complex causes and possible cures, for the current crisis, mindful that the confluences of events and circumstances producing today's IG shortages will not yield to simple or quick solutions. Nor will the problem succumb to any form of subtle supply blackmail, in which safety concessions are extorted from regulators and patients to gain increased supplies. Less rigorous compliance standards or reduced vigilance against infection agents will not solve today's problem, and could cause more serious shortages tomorrow.

Once again, the subcommittee is honored to welcome David Satcher, who has been our steadfast partner on public health issues, both as Surgeon General and in his previous capacity as head of the Centers for Disease Control [CDC]. His participation today underscores the importance of this issue, and the unified public health response needed to address it.

All our witnesses today are welcome and appreciated, and they have been asked to describe near-term solutions to direct scarce supplies to critical patients, as well as long-term proposals to increase IG production and prevent future shortages.

In this morning's session we will hear from the Surgeon General, the acting head of the FDA, Dr. Michael Friedman, the CDC, as well as patients and physicians coping with IG shortages. This afternoon, executives from all the major U.S. fractionation companies, a major IG distributor, the American Red Cross, and the Swiss Red Cross will testify on their efforts to meet critical demand for their products. We sincerely look forward to their testimony today.

And at this time I would call on Mr. Kucinich, if he has a statement.

Mr. KUCINICH. Thank you very much, Mr. Chairman and members of the panel. I'll yield to——

Mr. TOWNS. No; you can go ahead.

Mr. KUCINICH [continuing]. Ranking member, Mr. Towns, and members of the panel. As all of those on the panel know, but per-

haps not everyone who has just tuned into this issue is familiar, immune globulin is a protein extracted from blood plasma, rich in antibodies, and immune globulins are made from the large pools of plasma collected from human donors.

People ask, what are those products used for? Well, they're used to prevent measles, Hepatitis A in persons who have not been vaccinated, and they're used for the treatment of primary immuno-deficiency diseases, a group of 70 disorders in which immune system malfunction causes increased susceptibility to infection, auto-immune disease, and malignancy.

Immune globulins can be administered, as the doctors here know, intramuscularly or intravenously. We're here because a supply of intravenous immune globulins suddenly ran out in November 1997, and thousands of patients who required regular infusions were forced to skip their treatments or to reduce their dosages.

Of course, we know that the FDA took action and telephoned presidents and CEO's of all the intravenous immune globulin manufacturing companies—as many as there are, that is—and requested that they expedite releasing of existing product, and in turn the FDA promised to expedite the testing of products awaiting clearance before manufacture release, a process known as lot release. And I understand the FDA has reduced lot release time from 3 to 4 weeks to 2 to 3 days.

One of the things I know we'll be talking about today is the "Dear Doctor" letter to the Nation's physicians, and also the recent survey by the Immune Deficient Foundation, which I think is quite significant because it indicates that 80 percent of immune deficient patients are experiencing problems obtaining intravenous immune globulin, and 56 percent of these patients are experiencing adverse health effects as a result. And, of course, 87 percent of physicians treating immune deficient patients report difficulty in obtaining intravenous immune globulin.

I might comment, if there was a weakness in all of this, as I see it, perhaps the "Dear Doctor" letter wasn't strong enough in letting doctors know that the shortages are critical and not to prescribe the intravenous immune globulin for non-critical problems. I'd like to hear something about that today.

So, Chairman Shays is to be commended for calling this hearing because we have a public health crisis on our hands that needs to be rectified, and I'm hopeful this hearing will address some of the short-term and long-term problems which the public will face.

The production's biologics is really like no other business. It's very technical. We know it requires a tremendous investment and that the products have to be of a very high standard; they're highly perishable. And the current business climate, where speculation has high payoffs—I can see why not many companies would even want to be involved, but there might be a lesson learned from that, Mr. Chairman. And I would like to say that there are a number of options which I hope we will be discussing today.

And one thing in conclusion that I would like to point out: the FDA does not have the authority to redirect intravenous immune globulin to people whose lives depend on it. And one possibility I hope is discussed is that the Surgeon General will address the appropriateness of developing a protocol, first for identifying when a

public health crisis exists and, second, for giving the Surgeon General the authority to take necessary actions that the FDA apparently does not have.

And I want to thank, again, the chairman for calling this hearing.

Mr. SHAYS. I thank the gentleman. At this time I would call on the vice chairman, Mr. Snowbarger.

Mr. SNOWBARGER. Thank you, Mr. Chairman; just a few brief comments. During our April district work period, I had the privilege of going to one of these manufacturing facilities—Centeon, in Kankatee, IL—and to view the process, and what I came away with is that it's a highly complex process; it's a long-term process. But I also came away with the feeling that we have manufacturers that are concerned about the quality of their product and about the timeliness of it reaching the market.

Clearly, we're caught in that fine balance between having a safe product, but having a supplier product that's there to meet the demand. So I'm anxious to hear from the witnesses today, and I appreciate the chairman holding this hearing.

Mr. SHAYS. I thank the gentleman. At this time I recognize Mr. Towns, the ranking member, and a true equal partner in this process. Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. I really appreciate you holding this hearing today. It's a very important hearing, one in that I think we're sort of anxious and eager to hear from the witnesses.

Today, we will pay special attention to the immune globulin, which is used for the treatment of many immune deficiency disorders. Lacking immune protection, individuals become highly susceptible to small ailments and can die from catching a cold. However, this protection does not come cheap. The annual retail costs of treatment for an adult can range from $25,000 to $45,000.

Mr. Chairman, this subcommittee should be added to the list of causes. We have urged increased monitoring of contaminated blood and blood products. We have demanded that FDA take decisive action to ensure the safety of the blood supply. We did the right thing then, and I'm certain we'll do the right thing now. Our role in this system of checks and balances demands continued vigilance and determination. We must continue to demand the safety of blood supply.

The Blood Safety Advisory Committee recommended that Government and industry enter agreements to collect and disseminate information on production, distribution, and demand for blood products, improve management of the emergency supplies, and consider distribution on a most-needed basis.

Mr. Chairman, this kind of cooperation and general agreement does not occur often. We must encourage and support this effort. I want to thank you for holding today's hearing, again, and look forward to hearing the testimony of our witnesses.

And let me just sort of add one other thing, which I think, Mr. Chairman, is not talked about enough. It takes 200 days to produce IG. By contrast, it only takes 19 hours to produce a car. Within the United States, only a few companies produce IG. Any shut-down or slow-down could have devastating effects. These same companies

have a major impact on the worldwide market through contracts with foreign entities to serve a supply source. Some have expressed concerns about the ability of the United States to force an end to the foreign supplier contracts to meet our supply shortages. Mr. Chairman, such a position would not win friends in the international community and would cause turmoil and severe shortages worldwide.

Thank you very much, and I yield back.

Mr. SHAYS. I thank the gentleman. At this time I would recognize Mr. Pappas, also another valued member of the committee. Thank you.

Mr. PAPPAS. Mr. Chairman, thank you for holding this hearing today which will help identify the causes of the critical shortage of immune globulin in our country, and will hopefully shed light on steps we can take now to increase production.

As you know, many families around our country are suffering because of the simple lack of availability of immune globulin. The stories each of these families tells are heart-wrenching. Many patients who go without immune globulin describe chills, high fever, strep throat, pneumonia as just a few of the symptoms that they have to battle with every day.

I truly feel for people like Arnold Chate, the father of two children in Morristown, NJ, whose very lives may depend upon obtaining immune globulin infusions. Mr. Chate's children and all Americans deserve answers. They need to know when they can obtain more immune globulin, what is being done to combat the shortage, what caused the shortage, and how we can prevent something like this from happening in the future.

I want to commend you, Mr. Chairman, for leading the way and making sure these questions are answered. I also want to commend those companies and non-profit agencies that have been so cooperative with our subcommittee. It is important that an honest and good faith effort be put forth so we can see the shortage end. I look forward to hearing the testimony and learning more about efforts to combat the shortage.

And before I yield back, Mr. Chairman, I'm going to have to go out for awhile; I hope to return, but if I can't, would I be able to submit any questions in writing?

Mr. SHAYS. Without objection, so ordered.

Mr. PAPPAS. Thank you.

Mr. SHAYS. They will be submitted, and the witnesses will be requested to respond to them.

Let me just get a little housekeeping out of the way, before recognizing our distinguished panel and ask unanimous consent that all members of the subcommittee be permitted to place an opening statement in the record and that the record remain open for 3 days for that purpose, and without objection, so ordered. And also ask further unanimous consent that all witnesses be permitted to include their written statements in the record, and without objection, so ordered.

[The prepared statement of Hon. Henry A. Waxman follows:]

STATEMENT OF CONGRESSMAN HENRY A. WAXMAN
HOUSE GOVERNMENT REFORM & OVERSIGHT
SUBCOMMITEE ON HUMAN RESOURCES HEARING ON
IMMUNE GLOBULIN SHORTAGES: CAUSES AND CURES
Thursday, May 7, 1998

Mr. Chairman, I applaud you for convening this hearing. It is clear that a public health crisis has taken our country by surprise, one which threatens the health and safety of thousands. It is equally clear that this crisis is not the product of unavoidable circumstances.

Instead, I believe there is evidence that this crisis is the result of failures on the part of many crucial parties in the manufacture and regulation of immune globulin.

The companies testifying today failed on multiple occasions and in numerous ways to follow good manufacturing practices, thereby exposing the public to unsafe and contaminated products. They concealed these violations from the Food and Drug Administration (FDA). They failed to inform public health authorities in a timely manner of their dwindling stocks and rising back orders of immune globulin. And they have failed to do enough to ensure that the short supply of immune globulin is being used -- first and foremost -- for the most seriously ill patients and in a manner consistent with its approved medical uses.

I have serious concerns, as well, over the manner in which the FDA carried out its responsibilities in this matter. The agency failed to inspect manufacturers in a timely or rigorous manner. Violations went undetected and uncorrected. Belated action against these violations only contributed to the current shortage.

Just as serious was the Public Health Service's failure to anticipate the immune globulin shortage. Whether for lack of information or attention, patients with primary immune deficiencies and children with HIV and rare disorders are needlessly suffering today.

Like my colleagues, I am not interested in pointing fingers or laying blame. It is my expectation that our witnesses are here today with answers to our questions. But it is my hope that they are also prepared to commit to specific actions and obligations which will bring this shortage to an end and prevent its recurrence.

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Mr. SHAYS. Let me recognize our witnesses. This is truly a distinguished panel, and we're very grateful that all four are here. Dr. David Satcher, Surgeon General of the United States, U.S. Department of Health and Human Services, whom I've already recognized; Dr. Michael Friedman, Lead Deputy Commissioner, Food and Drug Administration, and I want to say to you, Dr. Friedman, you've come before our committee on many occasions and I've always been impressed with your testimony, as well as the cooperation we've received from your agency, and I mean that sincerely.

Dr. Stephen Ostroff, Associate Director for Epidemiologic Science, National Center for Infectious Diseases, Centers for Disease Control and Prevention; I believe this is the first time you've come before our committee, and I welcome you; and also, Bernice Steinhardt, Director, Health Services Quality and Public Health Issues, GAO, and we welcome you again. You're always a wonderful witness, and we appreciate having you here.

We're going to go in the order I called, and as you know, we swear in all of our witnesses, even Members of Congress when they testify. And I would ask you to rise and raise your right arm, and I will say thank you. For those who might respond, or who you think might respond, we'll ask them to swear-in and then we'll have you give your card if you testify.

[Witnesses sworn.]

Mr. SHAYS. And for the record, all have responded in the affirmative. Let me say, your testimony is very important. Do we have a clock that works? OK, the way it works, as you may recall, we've asked you to be around 5 minutes, but, frankly, between 5 and 10. We'll roll the clock over one more time because we want your testimony. We don't want you to summarize it too much, but after 10 the gavel will have a chance—even for you, Dr. Satcher. [Laughter.]

I've finally developed that courage. Well, welcome. Here you go.

STATEMENTS OF DAVID SATCHER, M.D., Ph.D, SURGEON GENERAL OF THE UNITED STATES AND ASSISTANT SECRETARY OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES; MICHAEL A. FRIEDMAN, M.D., LEAD DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; STEPHEN M. OSTROFF, M.D., ASSOCIATE DIRECTOR OF EPIDEMIOLOGIC SCIENCE, NATIONAL CENTER FOR INFECTIOUS DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND BERNICE STEINHARDT, DIRECTOR, HEALTH SERVICES QUALITY AND PUBLIC HEALTH ISSUES, HEALTH, EDUCATION, AND HUMAN SERVICES DIVISION, GENERAL ACCOUNTING OFFICE

Dr. SATCHER. Thank you very much, Mr. Chairman, and members of the subcommittee.

I am Dr. David Satcher, Surgeon General of the United States and Assistant Secretary for Health at the Department of Health and Human Services. We do appreciate this opportunity to appear before you today to testify about this shortage of immune globulin products. This is a very serious public health matter and clearly worthy of our attention.

As you know, I Chair the Blood Safety Committee of the Department of Health and Human Services, and that committee was formed by Secretary Shalala in 1995, because she had made the safety and availability of whole blood and blood products a priority. I think the issue that we're discussing today reflects the interaction among three issues that we've been concerned about: availability, safety, and trust as it relates to the blood supply. I think they are all factors in this hearing.

The Blood Safety Committee is currently reviewing the immune globulin shortage. Only a week ago, our Advisory Committee on Blood Safety, comprised of a variety of medical, legal, and ethical experts, conducted 2 days of hearings on the immune globulin situation. Their recommendations, attached to my written statement, are currently being reviewed by our Department.

Immune globulins are one of several classes of proteins derived from human plasma, the fluid, or non-cellular portion of circulating blood. Other important plasma-derived proteins of medical value include albumin, which we use, as you know, to treat burn victims, and clotting factors, which we use for hemophilia patients.

My focus today is on the two types of immune globulins used to prevent and treat infectious and inflammatory diseases. They are immune globulins used intravenously, as you've pointed out, and immune globulins used intramuscularly. Among the well-documented and approved FDA uses of IGIV are treatments of Primary Immunodeficiency, Immune-mediated Thrombocytopenia, Kawasaki disease, Bone Marrow Transplantation, B-cell Chronic Lymphocytic Leukemia, and Pediatric HIV–1 infection.

But it's interesting to note that there has been an increase in off-label use of IGIV that includes treatment of a large number of neurological disorders, autoimmune disorders, and hematological disorders, and this is a factor in our discussion today.

IGIM is primarily indicated for post-exposure prophylaxis against Hepatitis A. It has also been used to a limited extent for travelers requiring Hepatitis A prophylaxis, although since 1995, we've had the Hepatitis A vaccine, and that's now recommended for the travel prophylaxis as opposed to IGIM. IGIM is routinely needed by every local health department when dealing with a sporadic case of Hepatitis A. And I think we remember best last year in 1997, when Michigan had the problem with frozen strawberries and many school children were infected with Hepatitis A. It was very important to have available immune globulin to use in that situation. It's also used in children with primary immune deficiency, but IGIV is usually preferred to avoid having to administer large amounts intramuscularly.

Drug shortages arise from a variety of causes, and that includes the unavailability of raw materials, of packaging components, or sometimes from marketing decisions—as we will see—increased demand, manufacturing problems, and enforcement issues. Throughout much of 1977, the Department received sporadic reports about shortages of clotting factors, of immune globulin, and of albumin. Occasional calls about shortages are certainly not unusual, and they may reflect a local, transient market fluctuation. The effect on public health of a transient shortage often may be mitigated by the

use of a comparable product that's manufactured by another company.

It is the Department's policy to attempt to prevent or alleviate shortages of medically necessary products as best we can, given our legal authority. We are committed to assisting in making sure that there is available an adequate supply of products meeting the high quality standards.

The CDC was first alerted about shortages in IGIM in October 1994, when a State health department was having difficulty locating sufficient quantities of the product for a large number of people who had been exposed to a food handler with Hepatitis A. CDC assisted the State in meeting its IGIM demand. Upon contacting Armour Pharmaceutical Co., which is now Centeon, CDC learned that most of the company's production was going to the Department of Defense, which was routinely using IGIM as a prophylaxis for soldiers stationed around the world. Now this was prior to the approval of the Hepatitis A vaccine, and I think that's important.

There were other factors as well, including a new viral testing requirement for IGIM that caused withdrawal of untested lots and the cessation of production by one major manufacturer—and that gets to the interaction between availability and safety. Our public health agencies, both the CDC and the FDA, worked with industry to facilitate IGIM availability. In October 1997, we recognized the potential for another IGIM shortage, and we requested that all IGIM manufacturers increase production. In addition, FDA worked with one manufacturer to perform testing of tetanus immune globulin so the product could be used as a substitute for IGIM. The FDA also worked with two companies to file applications to produce additional products, and these applications were reviewed expeditiously—both, in fact, in approximately 1 month—and this facilitated increased production. Presently, the amount of IGIM being produced is enough to meet routine public health needs, but, as you will hear, the inventories are low and we are concerned that IGIM reserves would not be sufficient to meet the demands of an unanticipated public health crisis.

I will now turn our concerns to another immune globulin product, and that's IGIV. The current IGIV shortage is the result of many factors, including an increase in demand for the product, decreased production by manufacturers, as well as increased quarantines, withdrawals, and recalls due to manufacturing problems and the CJD issue, Creutzfeldt-Jakob Disease. Also, manufacturers have stated that they have diverted their resources to quality assurance programs for manufacturing, thus reducing production capabilities—again, the interaction between safety and availability. Overall, we estimate that supply of IGIV fell short of demand by about 20 percent in 1977. The demand for IGIV has been increasing by about 10 percent per year over the last 3 to 4 years. This increased demand results from both new approved indications and an increase in off-label use of IGIV.

Although hard data are not available, off-label use is now estimated by the Immune Deficiency Foundation and by many physicians at major centers to represent 50 to 70 percent of current IGIV use. It is worth noting, I think, that alternative therapies are avail-

able for many of the diseases for which IGIV is being used in an off-label manner.

As I said, there was reduced production in 1997. In fact one major manufacturer, Centeon, distributed a significantly reduced amount of product in 1997 as a result of several factors: a consent decree entered into because of a regulatory violation, and the release of contaminated products. Centeon decided on its own that it would shut down production and, at the same time, that it would halt distribution of the product. Centeon's production shut-down went beyond the corrective actions actually required or suggested by FDA. In fact, we estimate that although FDA did require a temporary cessation of distribution prior to May 1997, these decisions of the manufacturer alone accounted for 60 percent of the total 20 percent shortfall in this product.

Other manufacturers were similarly affected. While FDA made every effort to allow manufacturers to continue operating while they addressed regulatory problems, some companies with compliance problems made decisions to stop release and distribution of products and to shift resources to the compliance correction.

CJD is another contributing factor to this shortage. Multiple IGIV lots have been quarantined or withdrawn because of donors who, after donation, were identified as being at risk or of having developed CJD, and we've discussed this issue before this subcommittee before. Many of these lots were distributed and largely consumed before the withdrawal went into effect. However, substantial amounts of intermediate products not yet processed into final products were also withdrawn, and this severely affected the supply.

We believe that these decisions not to process CJD-implicated intermediates into products, with special labeling warning of the risks, had a major impact on product availability.

We understand that other manufacturers, including American Red Cross and Baxter, also did not reach their 1996 distribution levels, and we estimate the impact of this was probably about 20 percent of the shortfall. While other manufacturers reached or surpassed their 1996——

Mr. SHAYS. Dr. Satcher, what I would love you to do, if you would. You have your uniform, and I'm going to make an exception to those in uniform, I guess, but I would like you to just conclude by the export, since 10 minutes have gone by. So I am going to let you finish your statement; in other words, I'd like you to finish your statement, but if you would just address the export.

Dr. SATCHER. Finally——

Mr. SHAYS. Thank you. [Laughter.]

Dr. SATCHER [continuing]. We do have quantitative information about the fate of IGIV products. We do not have information about what happens to these products when they are outside of the distribution chain, so we can't say a lot about the impact of exports.

But, Mr. Chairman, we have identified shortages of immune globulin products, and to a reasonable extent we know how these shortages occurred. But we will not be satisfied until we have assurances that the shortage will be resolved and that future shortages will not readily occur.

And as I said earlier, we are reviewing the recommendations of the Advisory Committee on Blood Safety, and we will follow through and implement the appropriate actions. Thank you.

[The prepared statement of Dr. Satcher follows:]

Mr. Chairman, members of the Subcommittee, I am Dr. David Satcher, Surgeon General of the United States and Assistant Secretary for Health at the Department of Health and Human Services. Thank you for the opportunity to appear before you today to testify about the shortage of immune globulin products. This is a serious public health matter and clearly worthy of our attention.

As you know, I am the Chairman of the Blood Safety Committee of the Department of Health and Human Services. The Committee was formed by Secretary Shalala in 1995 because she has made the safety and availability of whole blood and blood products a priority.

The Blood Safety Committee is currently reviewing the immune globulin shortage. Only a week ago, our Advisory Committee on Blood Safety, comprised of a variety of medical, legal and ethical experts, conducted two days of hearings on the immune globulin situation. Their recommendations, attached to my written statement, are currently under review by the Department.

Immune globulins are one of several classes of proteins derived from human plasma, the fluid (non-cellular) portion of circulating blood. Other important plasma-derived proteins of medical value include albumin used to treat burn victims and clotting factors used to treat hemophiliacs.

My focus today is on the two types of immune globulins used to prevent and treat infectious and inflammatory diseases. They are immune globulin intravenous (IGIV) and immune globulin intramuscular (IGIM).

Among the well documented, FDA-approved uses for IGIV are treatment of Primary Immunodeficiency (PID), Immune-mediated Thrombocytopenia (ITP), Kawasaki disease, Bone Marrow Transplantation, B-cell Chronic Lymphocytic Leukemia, and Pediatric HIV-1 infection. There has been an increase in off-label uses of IGIV that includes treatment of a large number of neurological disorders, autoimmune diseases, and hematological disorders.

IGIM is primarily indicated for post-exposure prophylaxis against Hepatitis A. (It has also been used to a limited extent for travelers requiring Hepatitis A prophylaxis, although the hepatitis A vaccine, approved for use in 1995, is now recommended instead of IGIM). IGIM is routinely needed by every local health department when dealing with a sporadic case of hepatitis A and is particularly critical in the setting of an outbreak, such as in 1997, when individuals in Michigan developed hepatitis A after

eating contaminated frozen strawberries. It also is used in children with primary immune deficiency, but IGIV is usually preferred to avoid administration of large volumes intramuscularly.

Drug shortages arise from a variety of causes, such as the unavailability of raw materials or packaging components, marketing decisions, increased demand, manufacturing problems and enforcement issues. Throughout much of 1997, the Department received sporadic reports about shortages of clotting factors, immune globulins and albumin. Occasional calls about shortages are not unusual, and may reflect a local, transient, market fluctuation. The effect on public health of a transient shortage often may be mitigated by the use of a comparable product manufactured by another company.

It is the Department's 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 in making sure there is available an adequate supply of product meeting high quality standards.

The Centers for Disease Control and Prevention (CDC) was first alerted to shortages of IGIM in October 1994, when a State health department was having difficulty locating sufficient quantities of the product for a large number of people who had been exposed to a food handler with hepatitis A. CDC assisted the State in meeting its IGIM demand. Upon contacting Armour Pharmaceutical Company, now Centeon, CDC learned that most of the company's production was going to the Department of Defense, which was routinely using IGIM as a prophylaxis for soldiers stationed around the world. This was prior to the approval of the vaccine for Hepatitis A.

There were other factors as well, including new viral testing requirements for IGIM that caused withdrawal of untested lots and the cessation of production by one major manufacturer. Our public health agencies, CDC and FDA, worked with industry to facilitate IGIM availability. In October 1997, we recognized the potential for another IGIM shortage and requested all IGIM manufacturers to increase production. In addition, FDA worked with one manufacturer to perform testing on tetanus immune globulin so the product could be used as a substitute for IGIM. FDA also worked with two companies to file applications to produce additional product. These applications were reviewed expeditiously -- both in approximately one month -- to facilitate increased production. Presently,the amount of IGIM being produced is enough to meet routine public health needs, but because inventories remain low, we are concerned that IGIM reserves would not be sufficient to meet the demands of an unanticipated public health crisis.

I will now turn to our concerns about another immune globulin product: IGIV. The current IGIV shortage is the result of many factors, including increased demand for product, decreased production by the manufacturers, as well as increased quarantines, withdrawals and recalls due to manufacturing problems and CJD issues. Also, manufacturers have stated that they have diverted their resources to quality assurance programs from manufacturing, thus reducing production capabilities. Overall, we estimate that supply of IGIV fell short of demand by about 20% in 1997.

The demand for IGIV has been increasing by about 10% per year since 1994. This increased demand results from both new approved indications and an increase in off-label uses of IGIV. Although hard data are not available, off-label use is estimated by the Immune Deficiency Foundation and physicians at major centers to represent 50-70% of current IGIV use. It is worth noting that alternative therapies are available for many of the diseases for which IGIV is being used off-label.

As I said, there was reduced production in 1997. One major manufacturer, Centeon, distributed a significantly reduced amount of product in 1997. As a result of a consent decree entered into because of regulatory violations and the release of contaminated products, Centeon decided on its own that it would shut down production and, at the same time, halt distribution of the product. Centeon's production shut down went beyond corrective actions required or suggested by FDA. We estimate that although FDA did require a temporary cessation of distribution prior to May 1997, these decisions of the manufacturer alone accounted for 60% of the total 20% product shortfall.

Other manufacturers were similarly affected. While FDA made every effort to allow manufacturers to continue operating while they addressed regulatory problems, some companies with compliance problems made decisions to stop release and distribution of product and to shift resources to the compliance correction.

CJD is another contributing factor to the shortage. Multiple IGIV lots have been quarantined or withdrawn because of donors who, after donation, were identified as being at risk of, or as having developed, CJD. Many of these lots were distributed and largely consumed before the withdrawals went into effect. However, substantial amounts of intermediate product, not yet processed into final products, were also affected by the withdrawals and placed in quarantine. We believe that the manufacturer's decision not to process CJD-implicated intermediates into products released with special labeling is the primary impact of CJD on product availability.

We understand that other manufacturers, American Red Cross and Baxter, also did not reach 1996 distribution levels in 1997 because of quarantined CJD implicated in-process intermediates resulting in a reduction of final product, accounting for about 20% of the total 20% product shortfall. While other manufacturers reached or surpassed their 1996 distribution levels in 1997, it is likely that they could have produced more had they not been affected by compliance or CJD issues, again reflecting decisions made by the companies and not required by the Federal Government. CJD product could be distributed as long as it is risk-labeled, a complex marketing decision for many manufacturers. Other factors that contributed to the total 20% product shortfall in distribution include decisions to retain product for later distribution to cover periods of planned plant shutdown, and potentially, not packaging IGIV in vial sizes most efficient for use of product.

Export of IGIV is another factor that affects the amount of material available for domestic distribution. FDA does not monitor how much product is exported and does not require foreign distribution data to be provided. Manufacturers, however, voluntarily have told FDA that exports are not a major factor responsible for the shortage although the amount exported could relieve the shortage in the United States. Exports account for 0 to 29% of distributed product, depending on the manufacturer, according to information received by FDA. It was recently disclosed by an industry trade group, the International Plasma Products Industry Association, that exports from the major United States fractionators increased from 1996 to 1997 and accounted for about 20% of their marketed IGIV products.

Finally, we do not have quantitative information about the fate of the IGIV product once it is outside of the direct control of manufacturers. There may be product released to the market but held up in the distribution chain. That data is not captured by any FDA analysis.

Mr. Chairman, we have identified shortages of immune globulin products, and to a reasonable extent, we know how these shortages occurred. But I will not be satisfied until we have assurances that the shortage will be resolved and that future shortages will not readily occur. As I said earlier, we are reviewing recommendations of the Advisory Committee on Blood Safety, which call for greater collaboration between government and industry to reduce and prevent immune globulin shortages. At minimum, this collaboration will occur. I look forward to learning more about the problem through the information presented here today, and as always, I look forward to working with you and the other members of the Subcommittee. Thank you.

Advisory Committee on Blood Safety and Availability

April 28, 1998

Recommendations to Address Shortages in Plasma Derivatives

I. RECOMMENDATIONS FOR THE SHORT TERM

1. The Food and Drug Administration, the International Plasma Producers Industry Association, and individual manufacturers and distributors of plasma derivatives and their recombinant analogs should, on a monthly basis, collect and disseminate information on production, distribution, and demand for intravenous immunoglobulin, clotting factors, and alpha-1 antitrypsin.

2. The Department of Health and Human Services should explore, in collaboration with industry, health care providers, and appropriate consumer groups, methods to optimize and standardize allocation of available products in an equitable manner, including management of emergency supplies and programs that distribute products directly from manufacturers to registered consumers.

3. Industry should discuss triage of specific plasma derivatives to specific patient groups with the Food and Drug Administration, the Federal Trade Commission, health care providers, and appropriate consumer groups in order to promote accountability to the public of these practices.

4. Industry should explore with the Food and Drug Administration the possibility of importing additional supplies of intravenous and intramuscular immunoglobulin preparations.

5. Industry should explore with the Food and Drug Administration strategies for reallocating partially processed plasma materials from one manufacturer to another in order to optimize production of alpha-1 antitrypsin and other plasma derivatives.

6. Industry should explore with the Food and Drug Administration labeling and disclosure strategies which would increase product availability without compromising public safety and trust.

7. Industry and government should explore the impact of a temporary decrease in exportation of plasma derivatives while they are in short supply in the United States.

II. RECOMMENDATIONS FOR THE LONG TERM

1. Every effort should be made to make recombinant clotting factors available to all who would benefit them, and all barriers to conversion from human to recombinant clotting factors should be removed.

2. The National Institutes of Health should convene a Consensus Conference on the use of recombinant clotting factors for patients with bleeding disorders.

3. Industry should explore strategies for the development of reserve supplies of plasma derivatives and for their allocation during shortages.

4. The National Institutes of Health and industry should immediately evaluate alternative dosage schedules and alternative delivery systems for alpha-1 antitrypsin therapy, including prophylaxis strategies and strategies for treatment during acute exacerbations of disease, and accelerate the development of gene-based products and gene-directed therapies for alpha-1 antitrypsin deficiency.

5. The National Institutes of Health and industry should support the continued evaluation of the use and appropriate dose of intravenous immunoglobulins for indications where its benefit requires further delineation, and the results of these evaluations should be rapidly disseminated to the public.

6. Industry should work with the Food and Drug Administration to expand capacity sufficiently to meet anticipated demand for plasma derivatives.

7. Industry and government should jointly explore the antitrust implications of efforts to share data in order to prevent shortages.

Mr. SHAYS. Thank you very much. I'm just curious. Do you both have the same rank in uniform or is this——

Dr. FRIEDMAN. No, sir.

Mr. SHAYS. OK. [Laughter.]

Well, then you definitely won't be able to go over 10 minutes. [Laughter.]

Dr. FRIEDMAN. And rank does have its privilege. I will use less time than Dr. Satcher.

Dr. SATCHER. But it will not affect the scientific integrity of his testimony. [Laughter.]

Mr. SHAYS. Thank you. Dr. Friedman.

Dr. FRIEDMAN. Mr. Chairman, and subcommittee members, it's my privilege to represent the Food and Drug Administration here today. My colleagues and I also appreciate this opportunity to discuss the shortage of immune globulin products, and specifically, the efforts of FDA to respond to these shortages.

We are deeply concerned that medically necessary products are in short supply, and there are adverse health effects for the patients involved. It is agency policy to try to prevent or alleviate shortages of medically necessary products as best we can, given the framework of our legal authorities. Our actions are aimed at helping patients and their physicians obtain high quality medical products.

Throughout much of 1997, FDA received inquiries about shortages of clotting factors, immune globulins, and even albumin. These calls came from patients or their physicians who were unable to find the products that they needed at a particular point in time. Most of the complaints focused on supplies of immune globulins for intravenous administration, referred to as IGIV.

Dr. Satcher has provided an overview of the problem and what we think are its causes. I would only like to address FDA's role in the search for a solution, and this search is a collegial one, with the physicians involved, with the companies involved, with all the relevant parties.

As Dr. Satcher has noted, occasional shortages are not unusual and may reflect local transient market fluctuations. In November of last year, we began receiving a large number of calls from patients, physicians, distributors, major treatment centers, and consumer and patient groups, all complaining about the shortage. FDA did not have a precise estimate of the extent of the shortfall because of the limitations on the data collected, but industry sources suggested that there was about 20 percent less IGIV produced in 1997 than in 1996.

Although FDA recognizes that shortages presented a serious problem for patients, the agency was not able to fully and directly intercede. FDA is responsible for ensuring the quality, the safety, and efficacy of these products, and that includes overseeing the integrity of the manufacturing processes. While these are very important authorities, the agency lacks regulatory authority to control price, production, distribution, export, or stockpiling.

Nonetheless, the agency has been active. Last winter, as soon as widespread problems became evident, FDA reached out to the manufacturers to facilitate increased production and distribution of IGIV without compromising safety or efficacy of the product. In De-

cember, senior FDA officials held a series of telephone discussions with the CEO's from the six companies that manufacture IGIV for the United States. We wanted to know if they were having problems with manufacturing, if they were shipping the product out of the country, or whether they had additional capacity or products manufactured outside of the United States that could be used here to alleviate the shortage.

Now, you will hear later directly from the representatives of the companies, but what we were told at that time is that they were having manufacturing interruptions, or expected to have some, as they came into full compliance with FDA requirements. They also reported that there would be a shortage even if they were at full capacity, mostly because demand had risen so dramatically over the last few years, and Dr. Satcher has outlined some of the reasons for that.

The companies also said that exports were not the major cause of these shortages, although market data suggested that perhaps up to 20 percent of U.S. product is exported, which roughly was equivalent to the amount of lack that we had last year. At FDA's request, the companies agreed to set aside some IGIV product for emergency use, to establish toll-free phone lines so that patients and physicians could get access to these emergency supplies.

Two companies agreed to consider bringing in European-approved product under an investigational new drug application for emergency use in the United States. As of the current time that has not happened, but the current discussions are ongoing.

Even though the agency is trying to boost its supply, let me stress that the FDA will not step back from its appropriately stringent inspection efforts of the plasma fractionators. The American public expects not only an adequate supply of an essential product, but also a high quality product produced under good manufacturing practices. We believe that industry is full in agreement with that.

We believe that it would not be in the public's best health interest to lower standards for these products. That should not be interpreted, however, that we are rigid or complacent. FDA has been flexible in risk-assessment decisions with respect to balancing the theoretical; that is, the remote risk of potentially affected CJD donor to a pool of plasma with a known, immediate need for IVIG.

In addition, to address the issue of off-label use for these products, FDA sent a "Dear Doctor" letter in January to over 300 medical organizations. The letter alerted medical organizations and their physicians to the shortage problem and provided guidance for prioritizing the use of IGIV and limiting off-label use for less well-defined indications. The letter also included the toll-free numbers for the manufacturers that they had established just for emergencies.

FDA is considering increasing surveillance of product distribution to assess the long-range potential of a product shortage before it actually occurs. This would involve receiving product distribution reports more frequently and being able to assess trends in these data. The conclusion, though—I must frankly say—is that we expect this shortage to continue for many months.

Many of the underlying causes have not been fully resolved. In particular, a number of manufacturers are still in the process of

coming into full compliance with current good manufacturing practices, and they can describe for you their efforts in that regard. The corrective actions, unfortunately, have an impact on current production or release of product, but over the long term we are convinced this will ensure a safe and adequate supply of a necessary product.

Although the shortage has not disappeared, it does seem to have eased. Where FDA was receiving 10 to 20 phone calls a day to inquire or complain about the shortages, the agency now only receives a handful of calls a week. Nonetheless, we know that there are patients who still cannot find this product at a particular moment in time, and we are as concerned today about those patients as we were last winter.

Still, we will not rest until this problem is fully resolved. FDA will continue working with the manufacturers to boost supply to meet the demand, even as it continues to assure the high standards for safety and efficacy. Our patients and our citizens deserve nothing less.

I'll close my remarks here and will be happy, along with my colleagues, to respond to questions that you have later. Thank you, Mr. Chairman.

[The prepared statement of Dr. Friedman follows:]

I. INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Michael Friedman, Lead Deputy Commissioner of the Food and Drug Administration (FDA or Agency). I appreciate this opportunity to discuss the shortage of immune globulin products and the efforts of FDA to respond to the shortages. As a public health agency, we always are concerned when medically necessary products are in short supply with the potential for negatively impacting patients' health.

My testimony will concentrate on the shortage of immune globulin intravenous (human) (IGIV) as the supply problems with immune globulin intramuscular (human) (IGIM) are addressed by Dr. David Satcher, Department of Health and Human Services, and also are discussed by Dr. Stephen Ostroff, Centers for Disease Control and Prevention.

II. FDA ACTIONS IN RESPONSE TO IGIV SHORTAGE

Sporadic reports of IGIV shortages were received early in 1997. During most of 1997, FDA addressed requests for information from patients and physicians about product availability primarily by calling manufacturers to assess how much material they had in

inventory and informing the requester about potential sources of product.

By November 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 in obtaining sufficient amounts of IGIV. The phone calls were from many different sources, including: individual patients; distributors; major treatment centers such as Walter Reed Army Medical Center, Johns Hopkins University Hospital, and Duke University Medical Center; as well as from consumer and patient groups such as the Immune Deficiency Foundation. FDA inquiries to manufacturers, large distributors, and group purchasing organizations revealed that there was little product in inventory or available on the market nationwide.

In response to the continuing shortage reports of IGIV, during the third week of December 1997, Dr. Feigal, Mary Pendergast, then Senior Advisor to the Commissioner, and I spoke to the chief executive officers of the leading plasma derivative manufacturers tp convey our concern about the shortages and to learn more about the reasons for the shortage and to determine ways to increase supply and production. Some of the options that were discussed with the manufacturers included importing European-approved product for patient use in the United States under investigational new drug applications (IND) and setting up

toll-free hotline numbers and product supplies for urgent needs and consideration of limiting exports. The companies were asked to prioritize distribution of IGIV according to patient need. All of the companies agreed to establish emergency reserves of IGIV and toll-free hotlines for the public. Two companies agreed to explore bringing in European-approved product under INDs for patient use in the United States. We also asked the companies that FDA be kept informed about ongoing production efforts.

Since those calls, FDA also has been working closely with manufacturers to facilitate increased production and distribution without compromising the safety or efficacy of the products. This involves frequent discussions with industry about its plans to come into compliance with current Good Manufacturing Practices (GMPs) without significantly disrupting production schedules. FDA also has expedited review of license supplements related to manufacturing changes for IGIV to bring available products more quickly to the market. FDA's oversight of products entering the marketplace, known as the lot release process, has been shortened from 2-3 weeks to 3-5 days.

To assure that available product was utilized most efficiently, i.e., for disease conditions known to respond to IGIV treatment, FDA sent a "Dear Doctor" letter to over 300 medical organizations on January 28, 1998. The letter alerted medical organizations and their physicians to the shortage problem and provided

guidance for prioritizing the use of IGIV and limiting off-label use. The letter also included 1-800 numbers of manufacturers of IGIV so that doctors could obtain product for patient use on an emergency basis.

In response to the shortage, FDA has increased its efforts to monitor supply. FDA repeatedly has called manufacturers to assess how much IGIV is in shippable inventory. In some cases, this information has helped to identify situations where FDA could expedite regulatory review of lots pending release. On at least one occasion, there was no reported shippable inventory available from the major plasma fractionators. FDA was able to relieve the acute shortage by expediting the release of a few lots of IGIV that were pending.

FDA also issued an Import Bulletin (#57-B09) alerting FDA offices of the shortage of IGIV. The Import Bulletin identified two United States-licensed foreign manufacturers who may legally export IGIV to the United States for commercial distribution; provided guidance for emergency use requests for importing IGIV from unlicensed foreign sources for use in treatment of patients in the United States; and discussed FDA's enforcement discretion to release shipments of IGIV from unlicensed foreign sources that are not covered by an IND when the quantity and purpose are clearly for personal use.

FDA does not have the statutory authority to regulate the price of products that it oversees, the quantity of such products that manufacturers sell, or to whom manufacturers may sell their products. FDA is nevertheless concerned about the public health implications of sales decisions of manufacturers. The Agency does everything within its power to ensure that there are adequate supplies of safe and effective products for patients.

FDA has limited authority to compel a manufacturer to stop shipping a regulated product. FDA, of course, does have authority and has a variety of enforcement tools to take action against a company that is shipping a product that is adulterated, misbranded, or unapproved. For example, FDA has authority to seek a judicial injunction that enjoins a company from shipping a product that is adulterated because of current GMP violations.

FDA, however, does not have authority to prevent a company from shipping, including exporting, an approved product that is in compliance with the applicable laws and regulations. Similarly, FDA cannot simply compel a company to ship or sell a product domestically in lieu of export. (Even if such authority did exist, it would be difficult to enforce a "no exportation" rule down the chain of distribution.)

Although manufacturers have established 1-800 numbers for emergency purchase, the Agency has information from consumer

complaints that in some cases manufacturers agreed to provide products to physicians only if the hospital has entered into exclusive contractual obligations. For a period during March, product was not available even when calling the 1-800 numbers.

The phone calls to FDA regarding the unavailability of IGIV have decreased from the November 1997 levels of 10-20 per day to the current level of 5-6 per week. Forty percent more lots of IGIV have been released by FDA per month since November 1997 than released prior to November 1997. This increase, however, was partly due to the short term effects of the actions described above to get more product on the market, rather than an increase in production.

The shortage of IGIV continues, and probably will for some time, because many of the underlying causes have not been resolved. In particular, a number of manufacturers are in the process of coming into compliance with current GMPs and are implementing corrective actions to achieve compliance that have impacted production or release of product.

Modification of current recommendations for product withdrawals due to risk of Creutzfeld-Jakob Disease (CJD) may help to alleviate the shortage to some extent, and FDA is considering such modifications. Labeling products according to CJD risk may be one way of modifying the recommendations. Thus, products at

minimal potential risk may warrant a generic label, while those at higher potential risk may require a lot-specific warning label. Further modifications in our existing CJD recommendations should come about as we learn more about the transfusion risk through research and surveillance.

FDA will continue to meet with plasma fractionators on an on-going basis to investigate additional ways to improve product availability. FDA will further investigate why the 1-800 telephone numbers are not being used fully to help provide product. FDA also is considering increasing surveillance of product distribution to assess the long range potential of a product shortage before it actually occurs. This would involve receiving product distribution reports more frequently and trending the data.

III. AGENCY RESPONSE TO DRUG SHORTAGES

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 in making sure there is available an adequate supply of product meeting high quality standards. Each 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 shortage problems, assess the potential

public health impact, and propose steps to resolve each shortage issue.

FDA's primary means of identifying whether or not a shortage actually exists is to monitor the number and persistence of inquiries from consumers, manufacturers, and distributors. FDA does not monitor the exact amount of drug products (including IGIV and IGIM) on a routine basis. Actual distribution data from manufacturers is supplied to FDA by manufacturers as part of the reporting requirement regulations found at 21 CFR §600.81. These regulations require manufacturers to report data about product distribution in the United States. While these data do not give us "real time" information, or an estimate of product available in the marketplace, the data do provide information about the amount of product distributed in the United States market.

FDA obtains lot release data based for some plasma derivatives based on its approval of lots for release. Lot release is required only for selected products. Lot release data do not include the amount or volume of product in the lot, i.e., number of doses. Lots approved by FDA for release, however, may not be distributed by manufacturers for various reasons.

IV. THE PLASMA INDUSTRY

As you are aware, Mr. Chairman, there were problems in the past concerning inspections of plasma fractionators. As I testified last June, FDA has addressed these problems by instituting changes, both procedural and managerial, in the inspection of these facilities.

FDA transferred lead responsibility for periodic inspections of plasma fractionators (manufacturers who further process plasma and other blood derivative products) to the Office of Regulatory Affairs (ORA). Today inspections emphasize a complete assessment of compliance with GMPs, including an assessment of the manufacturer's procedures for handling, investigating, and notifying FDA of reports of adverse experiences. This transfer of inspectional responsibilities to ORA has advanced FDA's goals of regulatory consistency and efficiency across all regulated products by making the inspection process for fractionators comparable to that for other regulated products.

The new approach to inspections of plasma fractionators has resulted in more in-depth inspections and, we believe, in production on a higher quality of product. FDA's inspectional findings (documented on the Form 483s, the form used to report findings of the inspection) contain more substantive items including items previously which may only have been discussed

with a firm and not necessarily noted on the 483 in some cases. More warning letters have been issued, and two companies are presently under consent decree to ensure that the plasma products are manufactured under quality conditions.

As a result of these changes, plasma fractionators have been under increased enforcement scrutiny in the past year. We believe that such scrutiny is necessary to assure the purity and potency of plasma products. Quality is particularly important with blood and blood products. FDA can assist in speeding up the process, but we will not lower safety standards, or minimize or abolish compliance programs.

FDA can sometimes help to avert a crisis or minimize the harm to patients if a shortage does occur. FDA is sensitive to shortage issues when the Agency takes regulatory action against a company and will work with a company to avoid a shortage situation if at all possible. For example, if shutting down a plant while the manufacturer corrects problems could lead to a shortage of a medically necessary drug, the Agency might exempt a single production line from the shutdown to keep that drug available.

Plasma, as the underlying source materials used in the manufacturer of derivative products has inherent risks because many diseases are characterized by the presence of an infectious agent in the bloodstream which can be transmitted through blood

and blood products. Additionally the supply of plasma can be limited by the number of available donors.

The risk of CJD transmission through blood and blood products is considered to be theoretical based on the absence of any proven transmission. Nevertheless, FDA has acted proactively to recommend deferral of donors at increased risk for CJD and withdrawal of affected products. In August 1995 and again in December 1996, FDA issued a memorandum to all registered blood and plasma establishments and establishments engaged in manufacturing plasma derivatives concerning revised precautionary measures to reduce the possible risk of transmission of CJD by blood and blood products. It is important to note, however, that FDA also allows the distribution of CJD-implicated material as long as the product is labeled accordingly. The risk/benefit of the product must be on the label. One manufacturer has used such risk labeling during this shortage period. As noted above, the decision to use risk labeling is a complex one for manufacturers.

There currently is no test available to screen blood donors for the presence of CJD. In fact, there is still scientific controversy over the nature of the causative agent. Recently there have been a number of withdrawals of plasma products because of the identification of donors who contributed to the plasma pool who subsequently died of CJD or were identified as having been at risk for CJD. These withdrawals and related

quarantines are considered to have contributed to the present shortage of IGIV.

V. CONCLUSION

Mr. Chairman, FDA's primary concern is that no patient suffer needlessly. We will continue to do everything within our power so that patients will have safe and effective medical products needed to treat their conditions. We will maintain our commitment to GMPs. At the same time, FDA will continue to encourage companies to sustain levels of production that will provide adequate amounts of drug product to patients who depend on these medical products.

Mr. SHAYS. Thank you, Dr. Friedman. Dr. Ostroff.

Dr. OSTROFF. Thank you, Mr. Chairman, and members of the subcommittee.

What I will do briefly is discuss CDC's role in helping to assure a supply of intramuscular immune globulin, IGIM, to meet public health needs in the United States by amplifying some of the points mentioned by Dr. Satcher in his testimony. Each of these points is further elaborated upon in written testimony provided to the committee.

IGIM is different from IGIV in several important aspects. First, most of the IGIM supply in the United States is used to prevent Hepatitis A in persons exposed to this virus. This is known as post-exposure prophylaxis and is very different than the therapeutic use of IGIV for persons with immunodeficiencies. Recent estimates suggest that 75 to 80 percent of the U.S. supply is used for this purpose, with most of the rest used for pre-exposure prophylaxis of Hepatitis A and for persons with immune deficiencies who cannot use IGIV.

Because of these unique uses of IGIM, most is channeled to and purchased by State and local health departments for use in their routine communicable disease programs to limit the spread of Hepatitis A in the setting of a sporadic case of illness or during an outbreak of Hepatitis A.

Second, there are fewer producers of IGIM in the United States than those for IGIV. When shortages were first observed in late 1994, 95 percent of the civilian supply and 100 percent of the military supply was produced by one company, Armour Pharmaceutical, now known as Centeon, with a small amount produced by the Michigan Department of Public Health and more recently by the Massachusetts Department of Public Health.

The third difference is that there is an alternative to the use of IGIM for pre-exposure prophylaxis, that being the Hepatitis A vaccine which was licensed in the United States in 1995. IGIM shortages developed in late 1994 due to increased needs by the military to protect troops headed for overseas operations from Hepatitis A. This depleted the supply available to the civilian sector.

In response, CDC called together a group with representation from HHS, the Department of Defense, the State epidemiologists, and the two producing companies to help manage the available supply of IGIM. This group, which now includes the third producer, the Massachusetts Department of Public Health, continues to meet by telephone on an as-needed basis. This voluntary approach was possible because of the unique uses and distribution of IGIM and because of the public health roles played by CDC and the States in the control and prevention of Hepatitis A. Members of this group track the available supply, and CDC approves or denies orders over a threshold volume which has been agreed upon by the working group.

Even after the military instituted routine Hepatitis A vaccination in 1995, eliminating their need for IGIM, shortages have persisted because of requirements to screen lots of IGIM which have not been subjected to viral inactivation for the presence of blood-borne pathogens, specifically Hepatitis C virus, using gene amplification by the polymerase chain reaction, or PCR technique.

The first requirement, in late 1994, was for testing of all newly produced lots of product. This was extended in 1995 to unexpired lots which were already in distribution. In response, Centeon elected to withdraw the unexpired lots instead of conducting the testing, rapidly resulting in a shortage. In 1996, when a more sensitive PCR assay became available for Hepatitis C, the same sequence of events was repeated and, again, unexpired lots were withdrawn from the marketplace. These decisions meant only newly produced lots of IGIM were available for distribution, once they tested PCR negative.

In 1996, Centeon ceased production until they could market product which incorporates viral inactivation, something which has not yet occurred. As a result, the Michigan and Massachusetts Departments of Health became the only suppliers of IGIM in the United States. These suppliers have already expanded their capacity to virtually maximum production, and since 1996 routine and emergency needs of IGIM have been met with this limited supply.

In late 1997, when it was determined that the next lot of product from Michigan would be delayed based on unusual usage consumption patterns, we anticipated—or usual consumption patterns—we anticipated that the supply of IGIM would be exhausted before the next lot was available.

Working with FDA and Bayer Biologics, it was determined that tetanus immune globulin could be used as an alternative to IGIM. The company graciously made available a limited supply at a greatly reduced price, roughly equivalent to the price of IGIM, so that it could be purchased by our State and local partners during emergencies. In fact, there have been instances in 1998 where TIG has been used in place of IGIM.

At present, current production of IGIM is approximately 25 percent of what it was before the shortage began, and the two current producers have little ability to expand production. In spite of this unfortunate situation, over the past 4 years, when CDC assistance has been requested, we have always been able to deliver adequate prophylaxis, and we are unaware of any preventable cases of Hepatitis A which have resulted. This speaks to the success of the voluntary Federal, State, and industry interactions which have developed to deal with this situation.

However, this is balanced by the fact that despite these efforts, today the supply is as precarious as it has been at any time in the past 4 years. We are aware that Centeon, as well as Bayer, plan to join the market with fresh supplies of IGIM over the next few months and will hopefully create a necessary buffer in emergency situations. Coupled with wider use of Hepatitis A vaccine for pre-exposure situations, this should stabilize the supply of this critically needed biologic over the longer term.

Thank you for your attention, and I would be happy, along with my colleagues, to answer any questions.

[The prepared statement of Dr. Ostroff follows:]

Good morning. I am Dr. Stephen M. Ostroff, Associate Director for Epidemiologic Science, National Center for Infectious Diseases (NCID), Centers for Disease Control and Prevention (CDC). I am accompanied by Dr. Harold S. Margolis, Chief, Hepatitis Branch, Division of Viral and Rickettsial Diseases, NCID, CDC. I am pleased to be here to describe CDC's participation in efforts to ensure an adequate supply of immune globulin for intramuscular injection -- also called IMIG – to meet public health needs in the United States.

Immune Globulin for Intramuscular Injection (IMIG)

CDC and its State and local partners have a particular interest in the availability of IMIG because this product has a vital public health importance and widespread use in preventing infection with hepatitis A virus after exposure and in limiting transmission to others. As such, IMIG is routinely needed by every local health department when dealing with a sporadic case of hepatitis A and is particularly critical in the setting of an outbreak, such as in 1997, when individuals in Michigan developed hepatitis A after eating contaminated frozen strawberries.

IMIG is produced from pooled human plasma, and the final product contains immunoglobulins, or antibodies, that provide short term immunity against hepatitis A and other selected infections. IMIG is approved by the Food and Drug Administration (FDA) for various uses, including providing protection to persons who (1) are exposed to hepatitis A, (2) are exposed to measles and cannot be vaccinated with measles vaccine, (3) are traveling to countries where they are at risk of getting hepatitis A, or (4) lack antibodies due to certain immunodeficiency states. IMIG is a different product than intravenous immune globulin (IVIG), which is prepared from the same

plasma starting material but is formulated differently and not used for hepatitis A prevention, but for the clinical treatment of primary immunodeficiency and other FDA-approved conditions. CDC communicates with FDA on an on-going basis regarding blood safety issues, and we are aware of the concomitant shortages of IVIG.

Hepatitis A is a relatively common infectious disease in the United States with approximately 30,000 cases reported to CDC in 1997. Although exact figures are not available, it has been estimated that most of the IMIG produced in the United States has been used to prevent hepatitis A in exposed persons. It is the only product approved for this purpose. If IMIG is given within two weeks of exposure to a person with hepatitis A, there is approximately an 80% chance that it will prevent the disease. Giving treatment to prevent disease after exposure is called postexposure prophylaxis. Most often this occurs when persons are notified by local health departments that they were exposed to a reported case of hepatitis A. In circumstances where the reported case is a foodhandler or when outbreaks are occurring, large numbers of doses of IMIG may be required to control the situation and prevent additional cases.

Until recently, IMIG was the only prophylactic measure available to persons traveling to countries where hepatitis A infection is very common. However, the protection provided by IMIG lasts for only a three month period. If the person traveled again at a later date, or stayed in a country for longer than three months, another dose of IMIG had to be administered. In March 1995, hepatitis A vaccine was licensed in the United States. CDC now recommends that travelers to countries with high rates of hepatitis A receive the vaccine, which provides

protection that lasts for many years and obviates the need for IMIG prophylaxis in this population.

IMIG Shortage

In late 1994, CDC became aware of a shortage of IMIG. The IMIG shortage is the result of a series of events which led first to an increased demand for the product and then to a decreased supply. Since becoming aware of the problem, CDC has responded to protect the public's health by working with our partners to minimize the impact of the shortage.

In October 1994, a State health department first alerted CDC of a possible shortage when that State was having difficulty locating sufficient quantities of IMIG to administer to a large number of persons exposed to a foodhandler with hepatitis A. CDC assisted the State health department in finding enough IMIG to fill their immediate needs. Upon contacting Armour Pharmaceutical Company, which produced essentially all of the nation's IMIG, we found that most of their production was going to the Department of Defense (DOD) to fulfill contractual obligations. At the time, DOD routinely gave IMIG to troops being deployed to various parts of the world to protect them against hepatitis A. In addition, DOD was attempting to establish an adequate reserve of IMIG to meet its anticipated needs.

To further investigate the apparent shortage of IMIG, CDC identified current and previous manufacturers of IMIG and determined their current production capacity and future production plans. In 1994, only two manufacturers were producing IMIG in the United States, Armour

Pharmaceutical Company and the Michigan Department of Public Health. Armour produced approximately 95% of the United States supply of IMIG for the civilian sector, and 100% of the supply for the military. However, Armour estimated that most of their production capacity would be going to DOD until mid-1995, leaving little supply for ongoing civilian needs. In late 1994, Armour had back orders from the civilian sector that approximated one year's production of IMIG.

In response, CDC established a working group which included decision makers from the two manufacturers, DOD, FDA, the National Vaccine Program, and the Council of State and Territorial Epidemiologists (CSTE). This group estimated the extent of supplies of IMIG that existed in the civilian sector and the production capacity for IMIG, and determined the potential impact of a worsening shortage. After extensive discussions by the working group, a voluntary plan was agreed to by all participants that would ensure efficient and equitable distribution of IMIG supplies for both the civilian and military sectors. The components and consequences of this plan were (1) that all back orders for IMIG were canceled by the manufacturers; (2) that the Michigan Department of Health increased production to its maximum capacity, all of which would go to the civilian sector to meet the projected ongoing needs; (3) that DOD would allow Armour to provide some IMIG for use in the civilian sector, dependent on the needs of DOD; (4) that the maximum number of doses ordered in a single month was limited and the medical and public health validity of orders that exceeded the limit would be approved by a CDC epidemiologist, on call 24 hours a day; and (5) that DOD, to the extent possible, would provide IMIG for those situations where the civilian supply was depleted, after review by CDC.

In January 1995, CDC sent a memo notifying State epidemiologists and health officers of this plan, and this information was placed on CDC's hepatitis telephone hotline. In the months that followed the implementation of this plan, the overall supply of IMIG remained limited because of increased DOD demands for the product. However, sufficient product was available for routine use and to fill large requests that met the established CDC guidelines for postexposure prophylaxis. CDC and the working group continued to monitor the situation, including production levels and distribution.

Product Withdrawls

In March 1995, two events occurred that affected the IMIG supply. One worsened the shortage, while the other reduced the demand for IMIG. First, FDA has been working since 1992 with the manufacturers to facilitate the addition of one or more viral inactivation or removal steps into the manufacture of all immune globulin products, including those administered intramuscularly. At the time, the IMIG manufacturing processes of both producers did not include virus inactivation or removal steps. Although IMIG preparations licensed in the United States have not been implicated in the transmission of bloodborne infections, such as hepatitis C virus (HCV) infection, in December 1994, FDA began testing new lots for the presence of HCV RNA with the polymerase chain reaction (PCR), and only negative lots were permitted to be released. Less than 10% of tested lots were positive and this precautionary measure had little effect on the IMIG supply. However, in March 1995, FDA requested that manufacturers test samples from already distributed lots of IMIG and notify their consignees of the results. Rather than test already released product which had not yet expired and quarantine positive lots, as recommended by

FDA, Armour Pharmaceutical Company initiated a voluntary withdrawal of all unexpired lots of IMIG distributed before implementation of testing. This action effectively removed most of the IMIG that health departments and other health care providers had in reserve, and left agencies almost completely dependent on current month-to-month production.

Through a March 1995 memo sent to all State epidemiologists and public health laboratory directors, CDC provided further information and guidance on the significance and appropriate interpretation of FDA's request and Armour Pharmaceutical Company's response. This information was also available on CDC's hepatitis telephone hotline and CDC epidemiologists continued to be available for further consultation 24 hours a day.

Hepatitis A Vaccine

At the end of March 1995, hepatitis A vaccine became available following licensure by FDA. The vaccine is highly effective in preventing hepatitis A when given before exposure. Thus, hepatitis A vaccination provided the ideal alternative to IMIG for travelers to countries with high rates of hepatitis A. CDC announced the licensure of the vaccine in a July 1995 issue of the Mortality and Morbidity Weekly Report. By mid-1995, DOD began to implement hepatitis A vaccination of troops. As a result, DOD's IMIG requirements diminished dramatically, increasing the amount available to the civilian market. By convening the working group periodically, CDC continued to facilitate communication and played the central role in identifying additional IMIG when emergencies arose. For example, between July and October

1995, CDC contacted DOD on seven occasions to obtain emergency release of a total of over 6500 doses of IMIG.

Centeon's Production Suspension

In March 1996, FDA began testing immune globulin products for lot release using a more sensitive hepatitis C virus PCR technique (PCR2) and in June 1996 requested that manufacturers test all unexpired lots of IMIG using PCR2. On June 24, Armour Pharmaceutical Company, now called Centeon L.L.C., initiated a voluntary withdrawal of all unexpired lots of IMIG and indicated that it was suspending production of IMIG until its new viral inactivation process was validated and approved by FDA. In response to the withdrawal by Centeon, DOD suspended the use of all IMIG stocks, thereby eliminating an important reserve for civilian emergencies, and directed accelerated hepatitis A vaccination of troops.

Centeon's cessation of IMIG production left the Michigan Department of Public Health, already working at capacity, as the sole producer. In July 1996, CDC convened a meeting of the working group and invited representatives from the Massachusetts Public Health Biologic Laboratories and the New England Region of the American Red Cross to participate. The Massachusetts Public Health Biologic Laboratories had recently received approval for manufacture of a virally-inactivated IMIG, and they were interested in distributing the product outside the state of Massachusetts. The working group developed a revised plan for the use and distribution of IMIG that included (1) making IMIG manufactured by Massachusetts available for purchase outside the state through its distributor, the New England Region of the American Red Cross; (2)

reducing the maximum size of orders that would be filled routinely, with requests for larger quantities continuing to require review by CDC; (3) the establishment of a contingency reserve of IMIG to be used for emergencies with the approval of CDC; and (4) reaffirming that with the availability of hepatitis A vaccine, IMIG should only be used for postexposure prophylaxis according to current CDC guidelines. Information concerning the anticipated worsening of the IMIG shortage and the plan developed by the working group was conveyed in writing to State epidemiologists in September 1996.

During the subsequent year, IMIG manufactured by the Michigan Department of Public Health or the Massachusetts Public Health Biologic Laboratories was distributed by the single commercial distributor of IMIG, FFF Enterprises of Temucula, CA, according to the prioritization algorithm developed by the working group. According to records maintained by FFF Enterprises, an average of approximately 12,000 2 ml vials per month were sold during this time. Although the contingency reserve could not be consistently maintained because the IMIG supply was sometimes exhausted by the time each new lot became available, CDC, in collaboration with CSTE, was able to identify sufficient IMIG for postexposure prophylaxis in all circumstances of which we were aware. This included providing approximately 25,000 doses to school children potentially exposed to hepatitis A during the outbreak associated with contaminated frozen strawberries.

Recent Availability of IMIG

In October 1997, CDC became aware of a planned delay in the production and release of the next IMIG lot from the Michigan Biologic Products Institute (formerly part of the Michigan Department of Public Health). The implications of this delayed release were that the IMIG supply might be completely depleted because Centeon had not resumed IMIG production. To respond to this potential emergency, CDC, FDA, and the manufacturers identified an alternative product, tetanus immune globulin (TIG), which could be used for hepatitis A postexposure prophylaxis if no IMIG were available. FDA worked with the manufacturer of TIG, Bayer Biologic Products, to complete the necessary testing to ensure equivalence with IMIG. Because the usual price of TIG would pose a financial hardship for State and local health departments, CDC worked with Bayer and the distributor to make a sufficient quantity of TIG available at a significantly reduced price for hepatitis A postexposure prophylaxis. CDC and CSTE provided guidance to State and local health departments regarding appropriate use of TIG if they could not find IMIG. The IMIG supply was completely depleted for a five-week period in January and February of 1998 and TIG was used for postexposure prophylaxis. CDC is not aware of any circumstances in which appropriate postexposure prophylaxis was not provided. TIG remains available should IMIG supplies become insufficient to meet public health needs.

To date, IMIG continues to be produced regularly by the Michigan Biologics Products Institute and also by the Massachusetts Public Health Biologic Laboratories, and distributed by the single commercial distributor according to the algorithm developed by the working group. This prioritization algorithm, combined with accelerated approval by FDA of lots submitted for

release and cooperation and communication between the manufacturers, the distributor, and CDC, has provided IMIG or TIG for postexposure prophylaxis in all circumstances of which we have been made aware.

According to records maintained by the distributor, approximately 275,000 2 ml vials of IMIG were shipped in 1997, of which approximately 70,000 (25%) were distributed to physicians for persons with immune deficiencies; the majority of the remainder was used to provide postexposure prophylaxis for hepatitis A. We estimate that this represents less than 25% of one year's production prior to 1995 and is the minimum amount necessary to respond for hepatitis A postexposure prophylaxis and to supply individuals with immune deficiency accustomed to using IMIG. Although usage of IMIG for some indications may have declined with the availability of hepatitis A vaccine, the nation's current IMIG requirements exceed production. Current IMIG inventory remains low.

Conclusions

In summary, IMIG has been in short supply in the United States for the past 3 and a half years. The shortage was initiated by the increased demand by DOD, which needed IMIG to provide protection for U.S. troops being deployed to foreign countries. In spite of the subsequent use of hepatitis A vaccine by DOD which virtually eliminated the need for IMIG by the military, the shortage has persisted because of a significant reduction in production. However, public and private sector stakeholders actively participated with CDC to develop stopgap measures. These solutions, which often had to be modified on short notice, appear to have provided IMIG to those

persons who required postexposure prophylaxis because of exposure to hepatitis A. While two manufacturers were able to increase IMIG production, a number of circumstances over the four year period left us today with a production level that is lower than it was in 1994. We understand that Centeon's new manufacturing process, which includes virus inactivation, has been approved by FDA, and it appears that Centeon will resume production in the foreseeable future. This will hopefully alleviate the short-term shortage.

As was the case with DOD in 1995, wider use of hepatitis A vaccine should reduce the need for IMIG prophylaxis in the United States. The Advisory Committee on Immunization Practices recommends hepatitis A vaccination for persons who are at increased risk for infection and for any person wishing to obtain immunity, including international travelers and others at high risk, such as children in communities with high rates of hepatitis A, men who have sex with men, and persons with clotting factor disorders. Increasing the vaccine coverage in the targeted populations is an important strategy to control hepatitis A and limit the need for IMIG. In addition, CDC will continue to work with State and local health departments, other Federal agencies, and other public and private partners to help minimize the impact the IMIG shortage has on the public's health.

Thank you very much for your attention. I will be happy to answer any questions that you may have.

Mr. SHAYS. Thank you, Dr. Ostroff. We'll now ask Bernice Steinhardt to make her statement.

Ms. STEINHARDT. Thanks very much, Mr. Chairman, and members of the subcommittee. We always appreciate the opportunity to appear before you. This morning we are here to report to you on the results of the study we undertook at your request. I'm joined by my colleagues, Marcia Crosse and Kurt Kroemer.

You asked us to look at the extent to which manufacturer recalls and withdrawals might account for current shortages of plasma products, in particular intravenous immune globulin, or IVIG. What we found was that the amount of product that has been returned following these actions has been only a small portion of the products distributed, particularly for IVIG. In general, once products were distributed, very little was returned.

Looking just at what's happened with IVIG, in the last 16 months there have been 2 recalls and 26 withdrawals. But adding up all these cases, the amount of IVIG actually retrieved thus far represents only about 1 percent of the total that was distributed last year. In the 2 recall cases, about 1,800 vials have been returned or destroyed, or about 15 percent of the 12,000 vials of IVIG that were recalled. But those 1,800 vials contained an amount equal to only about one-half of 1 percent of the total 16 million grams that manufacturers told us they had distributed in the United States in 1997. What's more, both of the recalls occurred in the spring of 1997 before there were reports of severe shortages of IVIG.

The 26 withdrawals of IVIG were all associated with potential risk of Creutzfeldt-Jakob Disease, or CJD. As you know, FDA considers CJD risk to be a theoretical one since there have been no known cases of infection through blood transfusion. When manufacturers believe that there might be some potential risk for CJD—if, for example, it turned out that the donor had had human growth hormone at some point, for example, they can try to pull the product from distribution through a withdrawal action.

Withdrawals are normally associated with minor violations, so FDA doesn't monitor them as closely as they do recalls. Among other things, this means that manufacturers are not asked to report to FDA on the amount of product they retrieve following withdrawals, so we had to rely on the manufacturers themselves for data.

What we learned from them was that the proportion of withdrawn IVIG the four companies have been able to recover thus far has varied from a low of 0.25 percent in one withdrawal action to a high of 18 percent. Overall, they've recovered only 6 percent of the nearly 400,000 vials of IVIG that were withdrawn. But more importantly, this amounts to only about 1 percent, 161,000 grams of the total immune globulin that was distributed in the United States last year.

As far as other plasma products are concerned—albumin, clotting factors, and so on—the story is much the same. Most of what was recalled or withdrawn has not been pulled from distribution, in many cases because it was already used. A little over one-third of all plasma products that were recalled in 1997 have been returned

or destroyed, and only 2 percent of the plasma products other than IVIG that were withdrawn have actually been retrieved.

So, again, to reiterate, recalls and withdrawals by themselves do not seem to account for a significant loss of IVIG or other plasma products from the market. Manufacturers told us that they also lost from 5 to 10 percent of their IVIG production because they had to quarantine or destroy plasma with CJD risk in the process of manufacturing, but we didn't verify these amounts.

You also asked us to consider the effect that reducing pool sizes might have had on the current shortage of IVIG. As you know, after your hearing last July manufacturers voluntarily agreed to limit to 60,000 the number of different donors whose plasma could be used in a single production run. But whatever the effects of this change may be eventually, it doesn't seem related to any current shortages. For one thing, the change in pool sizes weren't fully implemented until January 1998—January of this year—whereas the reports of IVIG shortages were first noted in November 1997. And since it takes about 6 months for manufacture, the products being released for distribution in November would have begun manufacture around April or May 1997, long before the pool size changes would have gone into effect.

Let me conclude my summary, there, Mr. Chairman, and I would be happy to answer any questions.

[The prepared statement of Ms. Steinhardt follows:]

Mr. Chairman and Members of the Subcommittee:

We appreciate the opportunity to be here this morning to discuss our examination of plasma product recalls and withdrawals. Plasma is the liquid portion of blood, containing nutrients, electrolytes (dissolved salts), gases, albumin, clotting factors, hormones, and wastes. Many different components of plasma are used for medical treatment, from treating the trauma of burns and surgery to replacing blood elements that are lacking as a result of disease, such as hemophilia. It is estimated that each year some half million people receive products manufactured from human plasma, including over 20,000 who receive intravenous immune globulin (IVIG).

In the past 6 months, there have been reported shortages in certain plasma products, particularly the immune globulins. Many different factors have been cited as possible causes of the current shortage, including recalls and withdrawals of plasma products, delays in production due to problems in compliance with the Food and Drug Administration's (FDA) current good manufacturing practices, and increased demand due partly to new uses of the products.

You asked that we review the first of these possible causes--recalls and withdrawals--to determine the amount of plasma products, and in particular, the amount of IVIG, that was being lost due to removal of products from the market. Recalls are used to remove products from the market that violate the laws or are defective, while withdrawals are used to remove products that present only minor or unknown risks or are removed completely at the manufacturer's discretion. Specifically, you asked us to report on the number of recent product recalls and withdrawals, the reasons for these actions, the different types of plasma products affected, and the amount of product that has been returned as a result of these actions. You also asked that we examine the impact on the current shortage of IVIG of reducing the number of donors for each plasma product.

To answer these questions, we obtained information from FDA and the major plasma product manufacturers.[1] Specifically, we obtained data on recalls from FDA, and because companies are not requested to provide FDA with data on market withdrawals,

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[1]The major manufacturers of plasma products distributed in the United States include Alpha Therapeutic, Baxter Healthcare, Bayer Corporation, Centeon, and the Swiss Red Cross. The American Red Cross collects and distributes plasma products, but its products are manufactured under contract by Baxter Healthcare and the Swiss Red Cross. For convenience, we discuss all of these entities as manufacturers. Together, these manufacturers account for over 95 percent of the production of plasma products.

we obtained these data from the manufacturers.[2] We sought information on all plasma product recalls and withdrawals from December 1996 through mid-April 1998.

In summary, the data showed that only a small proportion of distributed IVIG–about 1.1 percent–has been removed from the market as a result of recalls or withdrawals. However, only 5 percent of the vials of plasma products that were recalled or withdrawn has been retrieved to date. While additional quantities might still be retrieved, some portion of these products has already been transfused or is otherwise unretrievable. Further, changes to reduce the number of donors in each product appear unrelated to the current shortages.

During the period we reviewed, 11 manufacturers reported to FDA that they undertook a total of 12 recalls (affecting 33 lots of 7 types of plasma products) and 38 withdrawals (affecting 1,001 lots of 10 types of products). The reasons for the product recalls varied, but generally they related to specific manufacturing errors resulting in problems in product potency, sterility assurance, or incorrect labeling. The product withdrawals were all related to donors who were diagnosed with Creutzfeldt-Jakob disease (CJD) or were considered to be at increased risk for CJD.[3]

As reported to FDA, the proportion of IVIG vials retrieved following a recall was 15 percent, which amounted to less than 1 percent of the total IVIG distributed in 1997. In total, about one-third, or 38 percent, of the number of vials of all plasma products recalled has actually been retrieved from distribution or known to be destroyed. The proportion of distributed products retrieved following a withdrawal has been much lower. Data from the plasma product manufacturers showed 6 percent of the vials of IVIG that were withdrawn to actually have been recovered, representing 1 percent of the total product distributed in 1997. For other plasma products, the proportion of distributed vials retrieved following a withdrawal was 2 percent. Manufacturers also claim that their production of IVIG was reduced by 5 to 10 percent in 1997 because they had to quarantine or destroy plasma because of CJD risk, but these amounts cannot be verified.

BACKGROUND

Plasma products are manufactured through a process known as fractionation. This process separates the various active components of plasma, which are further manufactured into clotting factor products for hemophiliacs, albumin for burn and shock

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[2]Manufacturers are requested to notify FDA when they are recalling or withdrawing products from the market; they are requested to report to the agency on the amount of product returned under a recall, but not under a withdrawal.

[3]Creutzfeldt-Jakob disease is a degenerative neurologic disease that leads to progressive dementia and death.

victims, and immunoglobulin preparations for immune-deficient persons and to treat and prevent a variety of diseases. (See appendix.)

Most manufacturing facilities use large plasma pools to manufacture sufficient quantities of products. These plasma pools are derived by combining units from individual donations. The number of units combined into a common mixture for processing is known as "pool size." In the past, these plasma pools included as many as 400,000 donors, but recent steps to reduce the number of donors to which a patient may be exposed have led to reductions in the size of the plasma pools to the general range of 60,000 donors. Plasma used for plasma-derived products manufactured and distributed in the United States is donated only by U.S. donors in collection facilities licensed and registered with the FDA.[4]

Manufacturers must be licensed and registered with the FDA and must comply with regulations governing current good manufacturing practices. Each product must be separately licensed, and the manufacturing facilities are subject to FDA inspection. FDA regulations govern the recall or withdrawal of marketed plasma products.

Recalls are a manufacturer's removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers and against which the agency would initiate legal action–for example, seizures–if the product was not recalled. A recall is generally a voluntary action on the part of the manufacturer to protect the public from products that present a risk of injury or are otherwise defective, although FDA can order a recall if the manufacturer does not act. In any case, FDA monitors recalls and assesses the adequacy of a manufacturer's efforts in a recall. Among other checks, the recalling manufacturer is requested to submit periodic recall status reports to the appropriate FDA district office so that the agency can assess the progress of the recall.

Withdrawals are defined as a manufacturer's removal or correction of a distributed product that involves a violation not subject to legal action by the FDA or that involves no violation, such as normal stock rotation practices, routine equipment adjustments, and repairs. Companies are not requested to submit information on products retrieved under voluntary market withdrawals. FDA has stated that it does not routinely request such information because it focuses its limited resources in areas in which the risk to the public health is viewed to be the most significant.

FDA classifies actions to remove products from the market due to CJD risks as voluntary market withdrawals because the products are not considered to be in violation of the regulations and laws administered by FDA. Because there are no known cases of

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[4]Plasma products manufactured by the Swiss Red Cross for distribution in the United States use plasma obtained from the American Red Cross, the New York Blood Center, and other blood establishments in the United States.

CJD transmission resulting from blood transfusion, FDA concluded that the risk of transmission of CJD by blood components and plasma derivatives is theoretical. The agency has nevertheless been developing a policy that recommends the exclusion of donors at risk for CJD and the withdrawal of blood components and plasma products prepared from such donors.

Since FDA issued a memorandum to blood establishments in December 1996 stating this policy, many withdrawals of plasma products related to CJD risks have occurred. This memorandum noted that CJD may be acquired by exposure to infectious material[5] or may arise spontaneously at high frequency in persons with certain genetic mutations or at low frequency on an unknown basis. Those considered to be at increased risk include donors who have had blood relatives with CJD or have been told that their family is at an increased risk for CJD, those who have received pituitary-derived human growth hormone, and those who have received a dura mater graft.

The memorandum recommended that when blood establishments identify donors who were either subsequently diagnosed with CJD or at risk for CJD, plasma manufacturers should (1) immediately retrieve and quarantine products under the control of the blood establishment that were previously collected from the donor, (2) direct their consignees to immediately retrieve and quarantine any implicated products, and (3) quarantine and destroy any plasma derivatives.

RECALLS AND WITHDRAWALS HAVE NOT REMOVED SIGNIFICANT PORTIONS OF MARKETED PRODUCTS

The removal of marketed products through voluntary recalls and withdrawals has been widely cited as a major contributor to the current shortage. Our review determined that only a small portion of product has thus far been returned or destroyed in response to either of these types of actions.

Recalls Have Not Resulted in Significant Losses of IVIG

Manufacturers reported to FDA that they voluntarily initiated a total of 12 recalls of plasma products within the United States during the 16-month period we reviewed. Recalls were related to such issues as breaches in sterility, lots tested at less than full potency, and patients reporting hives after injection of a product. We obtained data for each of the recalls from FDA, including the number of vials distributed and the number of vials returned or destroyed. Details for each recall are provided in table 1.

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[5]Transmission of CJD has been documented to have occurred in transplants of infected dura mater or from treatments with pituitary-derived human growth hormone from an infected source. Dura mater is the fibrous membrane forming the outer sheathing of the brain.

Table 1: Plasma Product Recalls, December 23, 1996, to April 9, 1998

Product	Manufacturer	Date of recall	Number of vials recalled	Vials returned or destroyed	
				Number[a]	Percent
Rho (D) immune globulin	Ortho Diagnostic	Mar. 9, 1998	Unknown	Unknown	Unknown
Albumin	Bayer Corporation	Jan. 9, 1998	15,777	19	0.1%
Rho (D) immune globulin	Ortho Diagnostic	Oct. 16, 1997	60,975[b]	47,982	79
Antihemophilic factor	Baxter Healthcare	July 12, 1997	5,324	4,820	91
Rho (D) immune globulin	Bayer Corporation	June 26, 1997	41,190	284	0.7
Antihemophilic factor	Baxter Healthcare	May 24, 1997	18,116	7079	39
Cytomegalovirus immune globulin	Massachusetts Public Health Biologic Labs	May 6, 1997	3,677	28	0.8
Immune globulin (IV)	Baxter Healthcare	Apr. 23, 1997	10,173	480	5
Immune globulin (IV)	Alpha Therapeutic	Mar. 7, 1997	2,189	1,363	62
Coagulation factor IX	Centeon	Feb. 28, 1997	883	546	62
Thrombin	Parke-Davis	Feb. 27, 1997	5,915	1,062	18
Antihemophilic factor	Centeon	Feb. 21, 1997	1,908	28	1
Total[c]			**166,127**	**63,691**	**38%**

[a]As of April 1998.

[b]Recall of this Rho (D) immune globulin is based on number of syringes (not vials).

[c]Totals do not include the most recent recall, for which the amount of product returned or destroyed is not yet available.

The proportion of product recovered or destroyed as of April 1998 varied widely across the separate recalls, ranging from a high of 91 percent to a low of 0.1 percent, with an average recovery rate per recall of 33 percent. However, the recovery rate was high enough on one large recall so that, of the total 166,127 vials recalled, some 38 percent had been returned or destroyed.

Two of the recalls involved IVIG: one because of a labeling problem, and the other because of a higher than expected rate of hives in the recipients. As a result of the two recalls, 15 percent of the vials have been returned or destroyed. This represented 0.07 percent of the total volume of 15.7 million grams of IVIG the manufacturers told us they distributed in the United States in 1997. Both IVIG recalls occurred in the spring of 1997, prior to reports of severe shortages in these products.

Only a Small Proportion of Product Listed for Withdrawal Has Been Recovered

From December 23, 1996, to April 9, 1998, manufacturers initiated 38 withdrawals of plasma products in the United States.[6] Among the major plasma manufacturers, the Swiss Red Cross had the most withdrawals announced during this period (16), while Alpha Therapeutic had only 1, and Centeon had none. Each withdrawal was related to donors who were at increased risk of CJD. Overall, only 3 percent of the vials withdrawn has been returned to manufacturers.

Twenty-six of the 38 withdrawals by four manufacturers involved at least some lots of IVIG. Of the 381,442 total vials withdrawn, only 23,404, or 6 percent, were recovered as of April 1998. The proportion withdrawn that was actually recovered varied from a low of 0.3 percent to a high of 18 percent across the different manufacturers. The portion retrieved amounts to 161,212 grams, which represented 1 percent of the 15.7 million grams of IVIG distributed in the United States in 1997. Information for each of the involved manufacturers is provided in table 2.

[6]Because companies are not required to provide FDA data on market withdrawals, we obtained data on the proportion of product withdrawn and, of that, the proportion recovered as of April 1998 from the manufacturers involved in these actions. We did not verify these figures.

Table 2: Withdrawals of IVIG, December 23, 1996, to April 9, 1998

Manufacturer	Number of withdrawals	Number of vials withdrawn	Number of vials returned[a]	Percent of vials returned
American Red Cross[b,c]	6	110,702	2,703	2%
Alpha Therapeutic	1	8,048	1,472	18
Baxter Healthcare[c]	5	109,942	312	0.3
Swiss Red Cross[d]	14	152,750	18,917	12
Total	**26**	**381,442**	**23,404**	**6%**

[a]As of April 1998.

[b]Data received from the American Red Cross represent 80 percent of the product they supplied (the other 20 percent is captured in the Swiss Red Cross data).

[c]In addition, the American Red Cross and Baxter Healthcare had withdrawals of fraction IV-1 paste and fraction IV-4 paste, which can be further processed into IVIG. It is unknown how much this would represent in terms of number of vials.

[d]These data include plasma obtained from and processed under contract for distribution by the American Red Cross.

Of the 38 withdrawals, 30 included plasma products other than IVIG. Some withdrawals were of a single product, while others involved multiple products. The withdrawn products included albumin, alpha-1 proteinase inhibitor, antihemophilic factor, coagulation factor IX, and plasma protein fraction. In addition, pastes that are distributed for further manufacture into plasma derivatives were also involved in some of the withdrawals.[7] Data related to the recovery of these other withdrawn plasma products are provided in table 3.

[7]Specific lots of fraction I+II+II paste, fraction IV-1 paste, and fraction IV-4 were variously involved in 12 of the withdrawals.

Table 3: Withdrawals of Other Plasma Products, December 23, 1996, to April 9, 1998

Manufacturer	Number of withdrawals	Number of vials withdrawn	Number of vials returned[a]	Percent of vials returned
American Red Cross	9	742,377	17,523	2%
Alpha Therapeutic	1	57,032	14,951	26
Baxter Healthcare	7	623,988	1,486	0.2
Bayer Corporation	7	131,011	3,800	3
Swiss Red Cross[b]	9	193,411	222[c]	0.1
Total	**30[d]**	**1,747,819**	**37,982**	**2%**

Note: Products include albumin, alpha-1 proteinase inhibitor, antihemophilic factor, coagulation factor IX, and plasma protein fraction.

[a]As of April 1998.

[b]These data include plasma obtained from and processed under contract for distribution by the American Red Cross.

[c]Information provided to us by the Swiss Red Cross noted that they did not know how many vials were returned for the vast majority of withdrawals of albumin.

[d]Some withdrawals involved multiple manufacturers.

Of the 1,747,819 vials of other plasma products that were listed for withdrawal, only 37,982 have been returned to the manufacturer. This represents a rate of 2 percent. When all the withdrawals are combined across the full set of products, including IVIG, only 3 percent of the total number of vials of distributed products that were sought have been returned.

Overall, of the 393,804 vials of IVIG the manufacturers attempted to remove from the market through either recalls or withdrawals, only 25,247 vials, or 6 percent of this amount, has been recovered, representing 1.1 percent of the total volume of IVIG distributed in 1997. Across all the plasma products that the manufacturers attempted to remove from the market through either recalls or withdrawals, of the 2,295,388 total vials sought, only 125,077 vials, or 5 percent of this amount, has been recovered.

The recalls and withdrawals represented attempts to recover products that had already been distributed. In addition to these distributed products, the FDA memorandum on CJD also calls for quarantine and destruction of plasma derivatives that are in production. The manufacturers have stated that their in-process losses due to CJD notifications have been significant. Three manufacturers provided data to us showing that they lost approximately 5 to 10 percent of their 1997 production of IVIG due to CJD risks. However, we did not verify these data.

CHANGES TO REDUCE THE NUMBER OF DONORS IN EACH PLASMA PRODUCT APPEAR UNRELATED TO CURRENT SHORTAGES

We also examined the impact of reducing the number of donors in each plasma product, which some plasma product suppliers have cited as contributing to the current shortage of IVIG. In testimony before this Subcommittee last July, the major plasma product manufacturers pledged to reduce the risk of transmission from infected donors by adopting voluntary restrictions on pool size and limiting to 60,000 the number of different donors whose plasma could be used in a single production run.[8] However, the manufacturers stated that it would take some time to implement the changes necessary to achieve such a reduction, and implementation of the policy was set for January 1998. Because the manufacture of plasma products takes approximately 6 months, products manufactured under the reduced plasma pool size restrictions are still in production and have not reached the market. In fact, the manufacturers told us that they expect it will be January 1999 before they finish distributing all plasma products manufactured prior to the pool size reductions. At the time that the severe shortage of IVIG was first noted in November 1997, plasma products being released for distribution were those that had begun production approximately 6 months earlier, around April to May 1997. Thus, the current shortages predate changes to reduce the number of donor exposures.

This concludes my prepared statement, Mr. Chairman. I will be happy to respond to any questions that you or Members of the Subcommittee may have.

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[8]"Food and Drug Administration Oversight: Blood Safety and the Implications of Pool Sizes in the Manufacture of Plasma Derivatives," hearing before the Subcommittee on Human Resources of the Committee on Government Reform and Oversight, House of Representatives, 105th Congress, First Session, July 31, 1997.

PLASMA PRODUCTS MANUFACTURED AND DISTRIBUTED IN THE UNITED STATES

Table 4 lists the plasma products manufactured and distributed in the United States and the primary uses of each.

Table 4: Plasma Components and Their Primary Uses

Component	Primary uses
Albumin	To restore plasma volume in treatment of shock, trauma, surgery, and burns
Alpha-1 proteinase inhibitor	To treat emphysema caused by genetic deficiency
Antihemophilic factor concentrate (factor VIII)	For prophylaxis and treatment of hemophilia A bleeding episodes
Anti-inhibitor coagulant complex	To treat bleeding episodes in the presence of factor VIII inhibitor
Antithrombin III	To prevent clotting and thromboembolism associated with liver disease, antithrombin III deficiency, and thromboembolism
Coagulation factor IX (human)	For prophylaxis and treatment of hemophilia B bleeding episodes and other bleeding disorders
Cytomegalovirus immune globulin	For passive immunization subsequent to exposure to cytomegalovirus
Factor IX complex	For prophylaxis and treatment of hemophilia B bleeding episodes and other bleeding disorders and for warfarin (anticoagulant) reversal
Hepatitis B immune globulin	For passive immunization subsequent to exposure to hepatitis B
Immune globulin: intravenous and intramuscular	To treat agamma- and hypogamma-globulinemia; for passive immunization for hepatitis A and measles
Plasma protein fraction	To restore plasma volume subsequent to shock, trauma, surgery, and burns

Rabies immune globulin	For passive immunization subsequent to exposure to rabies
Rho(D) immune globulin	To treat and prevent hemolytic disease of fetus and newborn infant stemming from Rh incompatibility and incompatible blood transfusions
Tetanus immune globulin	For passive immunization subsequent to exposure to tetanus
Vaccinia immune globulin	For passive immunization subsequent to exposure to smallpox
Varicella-zoster immune globulin	For passive immunization subsequent to exposure to chicken pox

Source: Adapted from the American Blood Resources Association, "Basic Facts About the Commercial Plasma Industry."

(108371)

Mr. SHAYS. Thank you very much. Were going to start with Mr. Snowbarger, then we'll go to Mr. Towns, and then I'll ask some questions; then we may do a second round or a third round. You have 10 minutes.

Mr. SNOWBARGER. First I have just a general question for the panel. Sometimes questions just kind of pop up in your mind and you think, "Oh, I think I may need to know the answer to that." And this may not be the right panel to ask, but obviously one of the concerns that we have, it would seem to me, is a shortage of any reserve supply, and one of you mentioned expiration dates. What kind of shelf life to these products have? Maybe Dr. Friedman.

Dr. FRIEDMAN. The question has really two answers. One is, it's about 2 years expiration date. That is how, however, largely a theoretical number since, as everyone has pointed out, what's being produced is being consumed with such rapidity. So I think that there is very little product which is lost because it exceeds the shelf life.

Mr. SNOWBARGER. Yes, and I guess my concern is not so much what is lost, but is there any incentive for manufacturers to produce a lot when potentially they're going to have to get rid of the product after 2 years if they've not been able to distribute it? So I mean——

Dr. FRIEDMAN. I think that's a question you can address to the manufacturers later. We've been impressed by the fact that for the last several years usage seems to have increased approximately 10 percent per year, so there seems to be a very active request for it.

Mr. SHAYS. Let me—sorry to interrupt. We have so many chairs here; I see people standing. I don't mind if the first four seats on both rows there are used and the first four there if anyone in either aisle wants to. Don't be reluctant to do it. Take the first four seats in either one there and in either side there. Please feel free to use them.

Mr. SNOWBARGER. Well, let me ask one more question. It seems——

Mr. SHAYS. Now, sir, excuse me. I'm going to have you sit on those four seats in the back there. That would be great; thank you.

Mr. SNOWBARGER. It seems I read in a very authoritative source—I think it was the New York Times—but—that the process, at least for some of these products, is like a 200-day process. Am I—again, I'll ask the manufacturers that as well if you don't feel comfortable with the question.

Dr. FRIEDMAN. My understanding is it's between 120 to 200 days, depending upon particular manufacturers.

Mr. SNOWBARGER. OK.

Dr. FRIEDMAN. Yes, sir.

Mr. SNOWBARGER. You talked earlier, Dr. Friedman, about your—we'll call it the "Dear Doctor" letter that went out about this, and I'd kind of like to followup on that and ask what impact that you observed from the physicians? Did they increase their prescriptions of IG, or did they change their processes to reflect the shortage?

Dr. FRIEDMAN. I'll ask my colleagues from the Center for Biologics if they would like to elaborate upon my answer. I think it's

very hard for us to assess exactly the impact that the "Dear Doctor" letter had, except that we believe that there was better utilization of the 1–800 numbers—the emergency numbers that had been set up with the companies. The reason we believe that is the volume of telephone calls to us decreased after that time, and we know that people still call us if they have great difficulty in obtaining the product.

So we know that at least part of the letter was effective in correcting the maldistribution between needs and supplies. Judging the most appropriate use of the product, only for those conditions where there's very good evidence, our means of assessing that are very imprecise, and we have impressions of that, but I don't believe we have good data on that. And I would ask Dr. Feigal, please.

Mr. SHAYS. Since, sir—when you leave, if you'd just make sure you leave a card with the recorder and identify who you are first, and your title.

Dr. FEIGAL. I'm David Feigal, the Medical Deputy Director of the Center for Biologics.

One thing that we heard at the Blood Safety and Availability Committee was actually testimony by different groups responsible for prioritizing the use of the products, which include third party payers, and there actually were groups that used our letter and other sources to help make decisions about how to prioritize. So, we don't have a direct way, but we have heard. The community that uses most of this product is relatively small, and I think they are trying to grapple with how to prioritize.

Mr. SNOWBARGER. Now my concern with the third party payers helping to make that decision is that is normally after the fact.

Dr. FEIGAL. No; actually we heard, for example, from a hospital consortium in Minnesota where they were actually controlling distribution at the time, and they prioritized it by the severity of the condition, how urgently the product would need to be used, whether it could be delayed, and they had a hierarchical approach. Just an example to cite, you know—one group that was able t intervene by prioritizing.

I think there are some opportunities with IVIG that are different than the intramuscular program because the patients with the most severe conditions tend to see a relatively smaller number of physicians, but the effort is just beginning to develop.

Mr. SNOWBARGER. Let me followup on that. Are the countries that we export these products to as prone to use them for off-label purposes as now we've found here in the United States?

Dr. FRIEDMAN. I'm not sure that we know that, sir.

Mr. SNOWBARGER. Has anybody tried to find out?

Dr. FRIEDMAN. Not that I'm aware.

Mr. SNOWBARGER. Let's move on to a different topic, and that is the issue of good manufacturing practices—and we're all laymen up here, and I guess it would be helpful to me to know. Can you give examples of what good manufacturing practices are, particularly ones that you've found that were not being met?

Dr. FRIEDMAN. Yes, sir; I can, and these will be generalities and won't be assigned to specific situations. Partly, it's the quality under which the product is manufactured, and partly it is the assurance that those practices are uniformly applied. So part of it is

recordkeeping that sterilization is occurring properly, that all the right things are done at the right time, and partly it's the quality of things like water.

We have had, sadly, some situations where we believe that improperly sterile water, not sterilized water, contributed to very serious infections that some patients had because of manufacturing processes that weren't as precise and under conditions that were as sterile and reproducible as possible.

We recognize that blood products have an inherent risk just because of the source of where they come from, and so we want to try and establish appropriately stringent criteria, but not impossibly stringent, because that wouldn't be in the public's interest at all.

Mr. SNOWBARGER. Well, that kind of moves me to what kind of corrective action is required in those circumstances? And let me compound the question here. In addition, what do you require the manufacturers to do—and I know it would depend on the violation. But are the requests that you make of the manufacturers the kind of thing that necessarily slow down their production?

Dr. FRIEDMAN. I think it depends upon the particular circumstances. If what is called for is validation of procedures, that is, to show that you're producing things in a certain uniform way under sterile conditions, then there is some time required to have product move through the plant, to make those assessments, to show that the care is proper in scrutinizing that product and controlling that product. So there certainly are built-in times when you are slowing down, or even in instances ceasing production while certain things are occurring.

Let me give you another example. If the quality of the water that's being used in the process is questionable or is shown to be infected with microorganisms, then you may have to stop the production, take a plant off-line, replace the water source or the filters or the sterilization equipment, and then start that process all over again. So, depending upon the violation there certainly can be interruptions, there certainly can be slowdowns, there certainly can be periods of ceasing production.

Mr. SNOWBARGER. Well, it gets us back to the statement I made in my opening remarks, and I would just ask the question to all of you since I don't have any time left. [Laughter.]

Mr. SHAYS. If you need a little more time——

Mr. SNOWBARGER. No, that's fine. I think the question we're all dealing with here is how you ensure that balance of safety and supply. Certainly, I don't think anybody wants to put out an unsafe product, and, at the same time, if we're holding the standards that are very rigid that slow down and even stop production and a manufacturer knows they're going to face that every so often, it's a little difficult to having any incentives to put out a large product base.

I mean I know manufacturers are just as concerned about liability issues as well, and so they want a safe product for that purpose, and it just seems to me that there's a real tension here between supply and safety.

Dr. FRIEDMAN. I think that's a very accurate assessment, and it's one that we pay considerable attention to. Recognizing that we

want to have the balance of having an available product, but also a product that's of high quality, is an ongoing balance that we're engaged in. We've looked very carefully at this, and this committee has been very active in this regard over the past several years. And we believe that the stringency of good manufacturing practices that we're calling for at this point are reasonable and are appropriate, and we do believe that the American public wants adequate supplies of blood products, but we believe that what they want—we're told that what they want—is high quality product. It's a difficult thing. It requires collegial interactions with the manufacturers and with the medical practitioners. It's difficult, but we believe that we are striking the right balance at this time.

Dr. SATCHER. I would just add I think that's why, and I tried to point it out at the beginning of my testimony, that I think this hearing is actually dealing with those three areas of our responsibility having to do with availability, safety, and trust. What does it take to have a blood supply that the American people can trust and feel comfortable with? What kind of standards are required? And as you're pointing out, those things can work against each other at times. And we have to be very careful to make sure that we don't compromise safety on the one hand, but at the same time we have a system that can meet the requirements of people.

In some cases the manufacturers have to decide what risks they're willing to take, as you implied, in terms of liability, because with CJD I think very clearly we don't have any evidence that it's transmitted in the blood, and manufacturers can decide to release it and to point out what the risks are, known and unknown. But it's a delicate balance.

Mr. SNOWBARGER. Thank you, Mr. Chairman. I didn't want to cut the other two off, but—thank you, Mr. Chairman.

Mr. SHAYS. OK; I thank the gentleman. Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me just begin by first trying to establish something here. I think, Ms. Steinhardt, that you said it takes about—for immune globulin to be produced—it takes about 180 days?

Ms. STEINHARDT. Six months.

Mr. TOWNS. Six months?

Ms. STEINHARDT. Right—the process. It's about 200 days—right.

Mr. TOWNS. 200 days? OK. I'm trying to figure out this discrepancy here I'm reading in the records. And why would we have such a discrepancy? Wouldn't we know how many days?

Ms. STEINHARDT. Well, I think these are based on manufacturer averages. We're all dealing with imprecise numbers, right.

Dr. SATCHER. Well, we just had a discussion about manufacturing and how rigid the rules are, and what certain manufacturers will do, and others; so that's why is varies.

Mr. TOWNS. That's why it varies; OK. Let me also clear up one other thing before we move on.

Dr. Friedman, you indicated the fact that the phone calls have decreased, so, therefore, you felt that the shortage was not as great?

Dr. FRIEDMAN. What I said was the number of phone calls to us have decreased significantly. What we believe is that there are patients and physicians who still have a very difficult time identify-

ing product, but that through the series of toll-free lines that have been established by the manufacturers that they or their physicians are ultimately getting the product that they need. We believe that there are instances where it's very difficult for patients and physicians to obtain the product, but with persistence they've been able to make those connections.

I fully recognize that this is indirect information, and I'm not saying that we're entirely confident of this conclusion, but we do believe that most patients are able to get the product after enough phone calls are made. We think that's an unacceptable situation—not just we, but everybody involved in this believes it's unacceptable. We want to have sufficient product easily available.

Mr. SHAYS. If the gentleman would yield.

Mr. TOWNS. I'd be glad to yield.

Mr. SHAYS. Just listening to your comment, it strikes me that you're saying that you're no longer getting the calls because the manufacturers are getting the calls, which is the only conclusion I think you can make.

Dr. FRIEDMAN. That's right, sir, except that if we believe, and I think with some reason, that if physicians or patients were unable to meet their needs, we would get calls; people would call us back. We've had some instances of that. We are looked at, I think, as the court of last resort in that sense. And so, again, I'm not trying to make too confident predictions based upon this incomplete information, but there were very severe situations last winter. We believe some of those situations have eased somewhat.

Mr. SHAYS. OK. Well, I can accept that you believe that, but when I heard your testimony, I had made the assumption that people had the same reason to contact you as they did before because they didn't have alternatives and that your calls were less. I then thought, well, that may just mean that people called you one time and they didn't feel there was a need to call you a second time, so you still had that group out there, and, plus, you were adding to that list. And now I find that it may even be less significant a statement because they now had somewhere else to contact and complain to, so——

Dr. SATCHER. I'd take it a step further, Mr. Chairman. I looked upon it not only as that the fact that if I call you and I don't get any results, I don't bother to call you back any more. That's the way we do congressional offices. [Laughter.]

If you call the office and you don't get any results, you just stop calling. [Laughter.]

Dr. FRIEDMAN. Well, again, I don't want to ascribe all the motives to all the people who are calling us. These calls are dealt with with such care and such sensitivity, and we are so serious about trying to meet the needs of patients, that I believe that if a patient or if a physician doesn't get the material that they need satisfactorily that they would call us back.

The second thing is that we know that there were emergency supplies set aside specifically for this, and so our hope is not unfounded that patients and physicians are getting the supplies they need. It's based upon the fact that manufacturers have committed to set aside emergency supplies for the most dire needs and that patients are drawing down on those supplies.

One manufacturer I think did the very appropriate thing of identifying lots of material that had this theoretic risk of CJD disease properly labeled. They were using that for their emergencies, as one component of their emergency supplies. That's the sort of flexible risk-based scientific strategy that all of us have had to resort to here.

Please understand—and I'll repeat myself—we are not satisfied with the situation. We take no comfort from the fact that we're getting fewer calls. I'm only reporting that to you. I'm saying I think the situation has to be when we get no calls, and until we're at that point, we're not satisfied and our job isn't done.

Mr. TOWNS. Thank you very much. Let me just sort of quickly—there's been some discussion around establishing priorities for use, at least until this whole shortage situation has been resolved. Can each of you explain whether you would support such an idea? And then if you support it, I guess I would have another question: How could it be enforced, Dr. Satcher?

Dr. SATCHER. I think in the appropriate situation we would certainly support establishing priorities. I'm not sure we can go to the next step and say how it would be enforced because I'm sure it would be some interaction between Congress and the Department that would determine that, but I think we have to be prepared to respond to crises, and crises, you know, demand that we act appropriately, and sometimes that does—that will mean setting priorities.

Dr. OSTROFF. Well, let me just say, at least speaking for the intramuscular immune globulin, that we have been setting those types of priorities for its use now since the shortages developed in late 1994. As it was mentioned, there are several different uses for the intramuscular immune globulin, some of which is for patient circumstances, for patients with immunodeficiencies that don't use the intravenous form of immune globulin, and they have always been the first priority for the therapeutic use of the product.

Then the second priorities have been for the post-exposure prophylaxis, when people have actually been exposed to somebody with Hepatitis A. That would be a priority over using it for pre-exposure prophylaxis, i.e., somebody who just happens to be traveling overseas and they're concerned that they may be exposed to Hepatitis A. So this is actually for the intramuscular product; this has actually been in place for quite awhile.

Dr. SATCHER. But voluntarily.

Dr. FRIEDMAN. On a voluntary basis; correct.

Dr. SATCHER. Not enforced.

Dr. OSTROFF. Right.

Dr. FRIEDMAN. The only thing that I would add, sir, is that for properly approved products that are available on the market, the Food and Drug Administration does not have authority to exert the sort of control that you're talking about. We're specifically proscribed from doing so, as long as those actions are consistent with a properly licensed physician carrying out what he or she believes to be the best standards of medical practice. So, we currently don't have any authorities to do that. What we do is to offer information, advice, and count on the oversight provided by a physician organization, patient groups, and so forth.

Mr. TOWNS. Yes; Ms. Steinhardt—thank you—yes. Do you want to comment on that? Yes.

Ms. STEINHARDT. Yes. I was going to say that to the extent CDC or FDA would want to implement such a policy, I think it would be very helpful for them to have a better base of information in which to make those kinds of decisions, because I think it was certainly apparent to us in our work, and I think FDA and CDC would agree that having information, having a good understanding, a more solid understanding of what the supply situation is, the extent to which product is in distribution, the extent to which product is taken out, is something that we're only beginning to deal with, kind of, at this point. So, I think having information is something we would have to—having a better base of information is something we would have to have in place in order to do something like this.

Mr. TOWNS. Right; thank you very much. Let me just—on this same note, in terms of looking at this whole shortage situation, to combat the high cost of AIDS drugs the Ryan White Act allows States to engage in volume purchases, which reduces the costs of the medicines. Would a program like this be helpful on the Federal level, at least until the shortage has been addressed—the bulk buy? Overseas purchase is what I'm talking about.

Dr. FRIEDMAN. There have been some consortia which have attempted to deal not only with the price issue, but contractual issues about supplies. I think that what you're posing—obviously Dr. Satcher will want to address this, I'm only pointing out to some extent these activities. Things like what you're talking about are being informally instituted currently, not on a State-by-State basis, but on a consortia hospital or practice basis.

Dr. SATCHER. I'm just—there certainly is a precedent for things similar to that in terms of vaccine purchase in the Vaccine for Children's program, so I think it would just depend upon the need. And I certainly agree with GAO that the issue here is really making sure that we have access to the information we need to make decisions, and in the context of a crisis, I think it's appropriate to do those kinds of things.

Mr. TOWNS. Mr. Chairman, my time has expired. I don't have anything to yield back. [Laughter.]

Mr. SHAYS. I'm trying to get a handle on this hearing and just get a sense of how I can put it in some perspective. We have four fractionator companies in the United States—one overseas that has a distributor in the United States. The company overseas draws on the blood supply from the United States. It's shipped to Switzerland; it comes back. I'm trying to understand what the appropriate relationship is with the Government and these companies, and I'm realizing how little I know. This wasn't an exam on what you know, but when we talked about the shelf life Dr. Friedman, and that it varies. So I'm gathering that each company has proprietary information——

Dr. FRIEDMAN. Yes.

Mr. SHAYS [continuing]. That would determine that their shelf life can vary from one to another. This goes beyond the hearing, but given we're talking about the blood supply and the safety of the blood supply, and so on, first off, does the FDA make a decision,

ultimately based on tests, on what the shelf life is of each of the companies' products?

Dr. FRIEDMAN. Sir, I'm not sure that that's exactly correct. I believe what we were talking about was the time required for production——

Mr. SHAYS. OK.

Dr. FRIEDMAN [continuing]. That varied. I'm not sure that we heard differences in shelf life.

Mr. SHAYS. OK; I misunderstood. What is the shelf life of these products?

Dr. FRIEDMAN. I'm told that it's roughly 2 years.

Mr. SHAYS. Why don't we have someone who can give me more than "roughly"?

Dr. FRIEDMAN. Dr. Epstein.

Mr. SHAYS. Would you give your full name, title?

Dr. EPSTEIN. My name is Jay Epstein. I'm Director of the Office of Blood Research and Review in the Center for Biologics at FDA.

The way we approach the dating period for products is we ask each independent manufacturer for validation on the stability of the product. You need to understand that not all the processes by which these similar products are made are identical, and therefore there can be differences in the stability which would lead to differences in dating. So, that's what accounts for variation, the fact that we have not stereotyped manufacturing. We do not mandate.

Mr. SHAYS. But in each case they've done the research and then you sign off on the shelf life?

Dr. EPSTEIN. That is correct. One of the things that we approve in the license is the dating period based on the stability data.

Mr. SHAYS. OK, and give me again the shelf life of immune globulin?

Dr. EPSTEIN. It's about 2 years for each of the immune globulin intravenous products.

Mr. SHAYS. It's pretty similar from one company?

Dr. EPSTEIN. Yes, it is.

Mr. SHAYS. OK; thank you. In the last hearing we had, and, again, Dr. Friedman, I was concerned that the Department was a little too willing to accept the private sector that you oversee—data, and work with them on certain issues that I thought was inappropriate. Do you remember what we had that dialog about? Does that ring a bell to you?

Dr. FRIEDMAN. I remember having the dialog. I don't remember the specific situation that we were talking about.

Mr. SHAYS. It was the basic acceptance. It dealt with, I think, enforcement of manufacturing processes. Was that the issue? I'd love someone to recall because——

Dr. FRIEDMAN. My memory is being jogged by this, yes.

Mr. SHAYS. OK, what was the issue that we were talking about? Because then I want to—whoever knows the answer to that question, please feel free to step up here. I wasn't intending to get in this area, but it seems to me that I need to get beyond this.

Dr. FRIEDMAN. I—granted the imprecision of my recollection of this—the manufacturers who certified that their processes were sufficiently sterile or their quality assurance was sufficiently intense, to the extent that those processes hadn't been inspected

carefully and critically reviewed, I believe—if I'm reconstructing this properly—was the concern that you raised. Our response at that time was that we were engaged in a very intense scrutiny of the plasma fractionating facilities in the United States and in Europe, which then send materials to the United States, and that we were looking very carefully at all the process validations and all the mechanical aspects of those facilities and that our intention was to have very high quality production and very reproducible quality assurance information.

We had evidence in the past where that had not always been attended to by the Food and Drug Administration and by the manufacturers as we thought was appropriate, and we were in the process at that hearing of vigorously correcting that. And I believe today we see the fruits that have been borne from that more careful assessment by ourselves and the manufacturers.

Mr. SHAYS. In our earlier hearing, we were looking at the contamination of the blood supply based on the infection of HIV AIDS and the hemophiliacs and the fact that they were kind of the canary in the coal mine. They contracted AIDS and many died. In that process there was this shadow figure, which was Hepatitis C, that we learned about—and 300,000 people infected.

And Dr. Satcher, we're very grateful to you and others for your coming and testifying and publicizing that information. I had two of my acquaintances contact me and say they learned that they had Hepatitis C.

What was disturbing to me about a hearing we had, Dr. Friedman, was that I didn't feel like there was the same kind of vigorous oversight of these infractionators with these five companies. And what I'm troubled by now, and I'm having a hard time articulating it, is it seems to me that we don't know much, that we don't know because it's proprietary information.

And I guess the first question I want to ask all of you is, what is the appropriate relationship that exists between the Government agencies and these five private companies? It's a general question, but I want to start there.

Dr. FRIEDMAN. Let me begin, if I may. I guess——

Mr. SHAYS. I'm going to ask all four of you this question.

Dr. FRIEDMAN. Yes, sir, and I would welcome comments from my colleagues here from the Center for Biologics. I don't think it's completely accurate to say that we really don't know what's in the companies. In fact, there is proprietary, there is commercial confidential information about these manufacturing procedures, but that does not affect our access to that information. And I believe the Food and Drug Administration does have proper access and complete access to the information that we need in order to inspect those facilities.

I clearly recognize this committee's interest and concerns about the quality of the products produced and the attention to good manufacturing practices. And I believe that the agency has been very attentive to those issues, not because this committee thought it was important, but because I think everybody thinks it's important. We certainly agree with you in that regard, and I believe that the new inspectional activities, the change in responsibility, the

kinds of things that we've been focusing on, really demonstrate this increased attention to the quality of the product produced.

We think that we should have very clear authorities with respect to how the product is manufactured, the quality of the product, the information that goes along with how best to use that product on the label. These, we believe, are important responsibilities that the public has entrusted us with.

There are other activities that this committee is focusing on today that I think are very important that we explicitly do not have responsibility for: how much is produced, where it's distributed, what is being charged for it, how much is being exported, management—company decisions about what they do with their product—that we have never had responsibility for and don't today.

Mr. SHAYS. OK, I'd like you just to repeat again the things that you don't have management of. Again, you did them so quickly I——

Dr. FRIEDMAN. I'm sorry.

Mr. SHAYS. No, you don't need to apologize. I just didn't write it down.

Dr. FRIEDMAN. That I don't have authority for. I will list these, I'll enumerate these, and then I'll ask my colleagues if I've left something out if they would please remind me of that. We do not have authority to regulate how much product is produced, how much is charged, what the cost of that product is, where that product is distributed—one State versus another, or how it is exported—one country versus another, how much is stockpiled or put aside for strategic purposes for the company.

Did I leave anything out? Of course; thank you. And I'm reminded that, of course, we don't speak about off-label use in an authoritative fashion, although we certainly do make recommendations, especially in this situation where there were shortages.

Mr. SHAYS. Thank you. That's a very helpful list. Thank you.

Dr. FRIEDMAN. Yes, sir.

Mr. SHAYS. Dr. Satcher.

Dr. SATCHER. I'll be brief. It's not an easy question to answer. The amount of regulatory authority that the FDA should have relative to these companies should, I think, be sufficient to protect the health of the American people. We are dealing with professionals, and in addition to, in terms of their preparation, it implies a level of professional responsibility, and so that gets into training and licensure and things like that.

But I think the bottom line is that whether we're dealing with FDA's ability to have oversight on manufacturing practices or the ability to regulate off-label use or exports, the bottom line should be the health of the American people and what does it take to protect that health.

The other thing that's interesting, and we've talked about this before, is the growing global implications of these discussions, whether you're talking about the global market and how it impacts upon the safety of blood in this country or the safety of food, or now the global impact on availability, sooner or later we have to deal with that.

I'm headed to Geneva, and one of the things we'll be doing is meeting with G–8 countries to talk about cooperating to deal with

the emerging infectious diseases. So weather you are talking about safety or availability, there are growing global implications, without question.

Mr. SHAYS. Thank you. Dr. Ostroff?

Dr. OSTROFF. I'll be very brief as well. I think that the interactions that we've had over the last 4 years with the producers of intramuscular immune globulin, again, has been totally on a voluntary basis. We also have no authority to impel them to produce, to sell at a particular price, or to make it available for specific uses.

I think one thing just to mention that's a little bit different is that, at least currently, as well as in the recent past, the suppliers of intramuscular immune globulin are not private sector, they're the Massachusetts Department of Public Health, as well as the Michigan Department of Public Health, and so the interactions and the relationships are probably a little bit different than they would be in the private sector. But we also have no authority or ability to impel them to provide, to stockpile, or to set their prices.

Mr. SHAYS. I felt—and this is my problem, not yours—that you were coming out of left field with the intramuscular, and I need to understand again why your emphasis was on the intramuscular.

Dr. OSTROFF. Yes; we've had very little—I mean we certainly have had discussions with the FDA about the circumstances of the intravenous immune globulin, but CDC is not an active participant in the issues related to IVIG to the extent that we are with the intramuscular, again because of the unique uses of IMIG as opposed to IVIG.

Dr. SATCHER. But we thought the experience with the intramuscular, since 1993, would help to inform this situation, and as Steve pointed out——

Mr. SHAYS. I see—the fact of how we've dealt with that.

Dr. SATCHER. Exactly; how we've dealt with it now for almost 4 years——

Mr. SHAYS. Yes; OK. Correct.

Dr. SATCHER [continuing]. As opposed to a problem that developed in November 1997.

Mr. SHAYS. That truly was your key point——

Dr. SATCHER. Exactly.

Mr. SHAYS [continuing]. And I'm sorry that it didn't sink in. Ms. Steinhardt. Remember, the question is concerning the appropriate relationship between the Government oversight and these five private companies.

Ms. STEINHARDT. Right, and I would say that—Dr. Friedman talked about the scope of FDA's authority. I would, without getting into the adequacy of the scope of their authority, I think that one question that we always look at is how well they use the authority they have. And one issue I mentioned before had to do with information, and certainly one of the questions that came to our mind here is how well they made use of the information that they did have—FDA has considerable data, actually—and whether they're managing the data to take into account or to anticipate potential shortages or critical needs.

Mr. SHAYS. Thank you. I'm going to conclude, and I appreciate the indulgence of my committee members.

The proprietary information you have, it's kept within your agency. That's the assumption I make.

Dr. FRIEDMAN. That's correct, sir.

Mr. SHAYS. Of these that Dr. Friedman listed—how many produced, how much charged, where it is distributed, how much is exported, how much is stockpiled, and off-label use, which do you think the Federal Government has the greatest need to inject itself in—how much produced, how much charged, where it is distributed, how much is exported, how much is stockpiled, and off-label use? Give me your first and second choice in terms of what would be a logical greater involvement by regulatory agencies.

And I'm going to go this way first to give you a little time to think.

Dr. FRIEDMAN. Thank you, Mr. Chairman. [Laughter.]

Mr. SHAYS. The only reason I did it is you looked very confused. [Laughter.]

Dr. FRIEDMAN. You were right.

Ms. STEINHARDT. Well, you mistook my relaxation for confidence. [Laughter.]

Mr. SHAYS. Dr. Satcher, how about you answering this question first?

Dr. SATCHER. Well, obviously we're dealing with a situation where I believe the off-label use of IGIV accounts for what—50 to 70 percent. So if you talk about the ability to have an impact on the problem, certainly the area of the off-label use of the drug is one, especially when, in many cases, we have alternative methods for treating those diseases. So, I would certainly look very hard at the issue of the role of FDA in off-label use of agents.

Dr. OSTROFF. Let me just say, CDC is not regulatory, but speaking strictly from the standpoint, again, of the intramuscular immune globulin, I think that our two greatest concerns would be with both production as well as stockpiling for emergency situations.

Mr. SHAYS. That's very helpful. Now my two on either end.

Dr. FRIEDMAN. Please.

Mr. SHAYS. The first time—you're being a gentleman now. [Laughter.]

Ms. STEINHARDT. Oh, I would defer to Dr. Friedman.

Dr. FRIEDMAN. I believe it's such a complex question, and it's filled with such subtlety and ambiguity that I'm not going to give you a specific answer, sir. And I don't do that because it isn't an important question, it's because it is a very large public policy question. I think——

Mr. SHAYS. OK, here's what I'm going to do. It's too much like a bureaucrat. I'm going to give you time——

Dr. FRIEDMAN. No, no, no; please let me——

Mr. SHAYS. No, I'm going to give you time to give me your top two, and you can qualify it and say that you have some uncertainties, but—Ms. Steinhardt.

Ms. STEINHARDT. Well, I feel that the work we've done here doesn't really support any recommendations for policy, but I want to say, again—make my first point, or reiterate the point I made earlier, which is that it's really important to see how well FDA makes use of the authorities that it has. I mean there's still—I

think it's a fair question to ask whether they're doing all that they can or doing as well as they can—today.

Mr. SHAYS. Yes, I want to be fair to you Dr. Friedman. I realize that in your position as Lead Deputy Commissioner and the fact that many people don't want the Government to regulate more. I'm not saying which you would ask to regulate; I'm just saying which is the one that. I'm going to give you a little flexibility here because I think it's deserved—but which is the one that this committee should look at as being an area that we should see what the Federal role should be?

Dr. Satcher was pretty specific, and Dr. Ostroff, you were pretty specific, and it related, obviously, to your expertise, so I would like to know.

Dr. FRIEDMAN. Speaking pragmatically and not talking about authorities specifically to accrue to the agency, what I would say is I'd agree with Dr. Satcher completely, given that off-label usage is the largest and least well-documented area, that would deserve attention. I have to also balance that though by saying that off-label usage is often the way in which new clues are identified for important new uses——

Mr. SHAYS. Right.

Dr. FRIEDMAN [continuing]. That sometimes are even more important than the uses that were on-label initially.

With respect to information in predicting things, I certainly agree with GAO, but I'm unaware of things that we could do today and would be happy for any suggestions from GAO or others to further improve this situation. We're looking very carefully at the data, but even when we look at data to help predict things that will happen in the future, we still, even when we can identify a problem, don't have the authorities to influence many of the things that we just talked about.

Mr. SHAYS. Thank you. My colleagues have been very patient with me, and at this time I would call on Mr. Snowbarger. Thank you, Mr. Snowbarger.

Mr. SNOWBARGER. Thank you, Mr. Chairman. In trying to get a handle on this, it's my understanding that the shortage for 1997 was in the neighborhood of 20 percent. About half of that was shortage of production and the other half an increase in demand. Does that give a rough picture in a way?

Dr. FRIEDMAN. Those are roughly correct, sir; yes.

Mr. SNOWBARGER. OK.

Dr. FRIEDMAN. We believe.

Mr. SNOWBARGER. Right. Dr. Satcher, I think you mentioned that the off-label use—and I couldn't quite tell what you were saying—is 50 to 70 percent of the increased growth, or use of the product?

Dr. SATCHER. Use of the product.

Mr. SNOWBARGER. OK.

Dr. SATCHER. And let me just—because I think in the former question the difficulty—and I appreciate FDA's cautiousness because they have to deal with these regulations. Production, I think, gets more to the issue of free enterprise than off-label use does, but they're both important to protect. But I think if we are in a crunch, I would certainly look at an area where we're dealing with 50 to 70 percent of the use, and we noted some of it is inappropriate.

Mr. SNOWBARGER. Well, let me go to off-label use, an area where we do have—Congress has—some potential for effecting policy. My understanding is that, and we have information that's provided by the Health Care Finance Administration, that it looks like they purchase roughly 13 percent of all the product. And let me just read some figures to you—they probably won't all stick—but in 1994 that purchase, or at least the allowed charges for IVIG, were $27 million; 1995, $41 million; 1996, $58.8 million, and 1997, $85 million—and that's with 95 percent of the precincts reporting. Oh, this is an election year; I'm sorry. [Laughter.]

Ninety-five percent of the claims filed, and they are already at $85 million, which is not quite, but it's coming pretty close. It's at least three times more than 1994, and coming close to four times. And my concern from the information from Health Care Finance Administration was that they apparently have increased their approval for off-label claims, which tells me that the problem of the shortage is not getting across the street to Health Care Finance Administration.

And if off-label usage is as significant a problem, Dr. Satcher, as you've indicated, it seems to me that might be the one place we can start in terms of trying to deal with that shortage.

Dr. FRIEDMAN. If I may just ask one question, and that is do we know that the increase in utilization was for off-label use? Because what had also happened during that time was there has been very vigorous research and actually more uses have been well-documented, and the number of labeled uses has also gone up importantly since 1994.

In addition, some of the conditions are more common. For example, its use in bone marrow transplantation. That is a technique that has been much more popular and much more widely employed. So you may well be right, sir, about off-label use, but part of it may be ascribed just to the larger number of well-documented uses and the popularity of certain techniques or procedures.

Mr. SNOWBARGER. Well, I think you're right. For instance, one of the areas mentioned specifically is kidney transplants.

Dr. FRIEDMAN. Yes, sir.

Mr. SNOWBARGER. I presume other organ transplants as well. No, I don't presume; I know what I'm talking about. That was—yes, you can strike that from the record. [Laughter.]

Dr. FRIEDMAN. And pediatric AIDS is another important area that's been better documented. More patients are receiving this, and so forth.

Mr. SNOWBARGER. OK; well that may be at least a partial answer to the question, but are any of you concerned? Have any of you done any research to find out to what extent HCFA's approval of off-label uses might be affecting this?

Dr. FRIEDMAN. We have not, sir.

Mr. SNOWBARGER. Mr. Chairman, I yield back.

Ms. STEINHARDT. We haven't either.

Mr. SNOWBARGER. I'm sorry.

Ms. STEINHARDT. But you know, just one caution about that. HCFA's approving—they're approving these off-label uses for reimbursement, which means that a patient could still make use of—you know, a physician might still order—and pay for it out of pock-

et. It just means that even if you changed HCFA's reimbursement policies, it may not necessarily change demand.

Mr. SHAYS. Thank you. At this time I would call on ranking member, Mr. Towns.

Mr. TOWNS. Thank you, Mr. Chairman, for the third round. There has been some discussion about using a warning label to notify people about the risk of CJD, instead of product withdrawal. I guess my question is, how would the use of such an alternative affect public health? Would this make a difference?

Dr. SATCHER. Let me just take a crack at that.

Mr. TOWNS. Let me just go and realign the question, and then maybe we can deal with all of it—and if so, how would it affect the price of the product, and how would it affect the supply of the product?

Well, go ahead and answer that, and then I'll—[laughter.]

You see, we're trying to learn as much as we can in this hearing; you know that.

Dr. SATCHER. Right. I'm just going begin this, I think. We've been talking about this interaction between the Government and manufacturers, and there is a third player here in the consumers. And basically what we're discussing is when you begin to transfer some of the decisions about safety and risk and the balancing of safety and risk to the consumer—and I think that that's what this is about—we know that we have not yet been able to document that CJD is transmitted to the blood, but there is that risk.

And so who takes the responsibility for that risk? I mean, is it the Government or is it the manufacturer? Or do we all three share it by saying, you know, this product is available but it does carry the risk of that it could transmit CJD? We could even communicate the magnitude of that risk and say and that, you know, this was a donor who received human growth factor, and therefore we can make some estimate about the magnitude of that risk. But there is that risk, and I think that's what we're talking about.

We're talking about sharing, you know, in this whole issue of the safety of the blood, balancing that with the availability and the trust. So we are getting to the trust now and how much of that burden we want to share with the consumer. So it's a good question, I think, and that's what we're talking about. We're talking about communication with the consumer about risk and availability.

Dr. FRIEDMAN. I would only that we all recognize the limitations of our knowledge with respect to CJD disease, and we can't make the sort of careful predictions and assessments that consumers and physicians would most like us to do. What we can convey, I think, is the best quality information that we have at any particular moment in time.

We've heard from patients who need intravenous immunoglobulin that a remote risk—10, 20, or some indefinable number of years later—is something that they are prepared to accept because of the urgent need for the product today. That's an informed choice. It recognizes the limitations of our knowledge. I respect the patient and the physician who make that choice or who make the opposite choice, which is to say that their particular need for the product

is not so great, or their fear of CJD is so great that they choose not to do so.

We have to optimize the public health benefit, given the limited scientific information we have. We can't step away from this responsibility, but we've heard from a lot of consumer groups who say, "Give us the information, even with its inadequacies. Let us make the choice." We respect that.

Dr. SATCHER. But let me just say, the issue of liability probably is still not clear because, as you know, what is decided in terms of liability is not left to us. It's left to the courts.

Dr. FRIEDMAN. There's one other thing I would add, which is you asked about price. I don't believe we can deal with that question, but I think that is a question that manufacturers would be better able to deal with. With respect to supply, we know that if some of this material is made available, it would help alleviate the shortage. No one of these things is going to completely alleviate the shortage. We have to optimize every component in order to try and provide sufficient material for patients who need it.

Mr. TOWNS. Let me just conclude by saying, Mr. Chairman, before you release the panel, is that I really appreciate, you know, the time that we're able to spend on this issue, and it's not a finger-pointing kind of thing. It's sort of looking for a specific kind of action to be able to improve the quality of care and lives, and I think that's what it's all about. So, I just want to convey that, even though some of the questions we kept going after, because the point is that we want to learn more about what's happening and what needs to be done. Maybe some action needs to be taken on this side.

Thank you very much, Mr. Chairman.

Mr. SHAYS. I thank the gentleman, and I just have a few more questions.

One, I want to know for the record, what are the implications of manufacturers' changes in the IGIV vial size? What are the implications of that?

Dr. FRIEDMAN. Again, I think that's a question that should also be addressed to the manufacturers later. The vial sizes are dictated by the manufacturing procedures. Whether a manufacturer chooses to use more of the larger-sized vials and fewer of the smaller-sized vials—for example, 10 milligram versus 5 milligram—those are decisions that are made really by the manufacturer uniquely. It's probably best to address those questions to the manufacturers.

Mr. SHAYS. Yes. What I really need to know is, you could just have wastage in the process.

Dr. FRIEDMAN. I'm sorry; yes, sir.

Mr. SHAYS. And the thing that bothers me about this is people are donating their blood, and I don't like the thought that you would waste any of it. And for me, from the outside looking in, people are asked to donate their blood; they're saying this is a public duty. And you have the private sector deal with it, and I want to make sure they're dealing with it in good faith.

Dr. SATCHER. This is an area of possible intervention, but I think we have to do it together.

Mr. SHAYS. Dr. Friedman, do you want to make another response?

Dr. FRIEDMAN. No, sir; I think not.

Mr. SHAYS. OK. But the bottom line is that if the vial size is too large for the individual needs, it is wasted material, correct?

Dr. FRIEDMAN. Well, that's correct, and the question is whether——

Mr. SHAYS. Does that trouble you?

Dr. FRIEDMAN [continuing]. Whether there is, given that there is shortage of supply, whether there's always the available vials to match the patient's size and need with the material that's available.

Mr. SHAYS. Well, tell me this. Even if there wasn't a shortage of supply, it was someone's blood that was donated. And if we have a wasteful process that means it just gets thrown out, wouldn't that be something that should concern us?

Dr. FRIEDMAN. I absolutely think it should concern us. I absolutely do, sir.

Mr. SHAYS. So it's not just a shortage.

Dr. FRIEDMAN. It's not just a shortage in an overall sense. It's a shortage in a personal sense, and if there is not material for a patient because what we do have is not being optimally utilized, that should concern all of us. That's correct.

Mr. SHAYS. Well, I know people who donate blood because they think there's a need for blood. If it's getting wasted, they wouldn't donate the blood.

Dr. FRIEDMAN. They still would.

Mr. SHAYS. No.

Dr. FRIEDMAN. I do it; you do it, but——

Mr. SHAYS. No, no; they wouldn't. Some people——

Dr. FRIEDMAN. But I think that we expect——

Mr. SHAYS. No, hold on a second. Dr. Friedman, hold on. I'll give you a chance to answer. I want to make sure you're hearing me. What I'm saying is that I think I can agree with you that if there's a shortage, it's a no-brainer. But I'm saying it goes beyond shortage, and I want to know how you think about this. I'm saying to you that most Americans don't know about these five companies. They don't know about how the plasma can be used for various very important medical uses. They probably just think that they donate blood and a transfusion goes to someone else. And they constantly hear about—not constantly, but often—hear about shortages.

Dr. FRIEDMAN. Yes.

Mr. SHAYS. And that impels them, as patriotic people—not just patriotic, but people who love humanity—to donate their blood. So I'm just saying to you that isn't there an added need to make sure, given that we aren't wasting it, whether or not there is a shortage?

Dr. FRIEDMAN. I now understand your point, sir, and I agree completely. I think that people want to know that their donation is being optimally used, absolutely.

Mr. SHAYS. Dr. Satcher, did you want to make a comment on that?

Dr. SATCHER. When I said this is a point of possible intervention—when you asked about what FDA could do—it may well be that in this scenario, that if necessary, we would look at it in terms of ways that we can impact upon availability.

Mr. SHAYS. Thank you. Dr. Friedman, in your statement on page 5, you said,

> Although manufacturers had established 1–800 numbers for emergency purchase, the agency has information from consumer complaints that in some cases manufacturers agreed to provide products to physicians only if the hospital has entered into exclusive contractual obligations.

Would you explain that to me?

Dr. FRIEDMAN. I would ask one of my colleagues, who actually has more direct knowledge of that than I. That is exactly what I was told.

Dr. Epstein, please.

Mr. SHAYS. Dr. Epstein, this is the second time you've testified, so thank you.

Dr. EPSTEIN. Thank you. FDA has on several occasions telephoned the 800 toll-free numbers to inquire whether product would be available for an emergency need. When we did this, particularly in March, we were informed by several of the manufacturers that product would only be made available if the individual or entity would agree to a long-term, sole-source contract for further supplies. That was not true for all the companies, but it was true for some of the companies.

Mr. SHAYS. Is that illegal?

Dr. EPSTEIN. I don't think I'm the one to comment on that.

Mr. SHAYS. I didn't say whether it should be. I asked if it was.

Dr. FRIEDMAN. My understanding from our counsel is that it is not illegal.

Mr. SHAYS. Well, I'm tempted to ask you to tell us what companies would do that, but I'm not going to do that. I would like the committee to have that information of what companies did that. I would compliment the agency on calling and learning how they deal with this, but now I want to know how you deal with it, if at all. You know, it raises some concerns. Thank you very much.

And this is the last question. It's a little more general. I want to know, since it didn't show up as one of the comments you made, how concerned I should be that Americans donate blood and their blood is exported overseas? I know we're all, as one of the company's representatives said—we're all God's children, and I do know that and I do know we have obligations.

I just need to know, given that we believe that there is not a shortage overseas, how concerned should I be that blood which is needed here is sent overseas?

Dr. FRIEDMAN. I'll be happy to give some preliminary remarks and then others can please add.

For products that are in adequate supply, obviously we care—I care little about the mercantile forces that affect that.

For products that are in short supply, I recognize the legitimate human needs of people all over the world, but I have to share with you a more parochial interest, which is I care most about our citizens. My agency is charged with the public health of American citizens, and so to the extent that we can, we want to optimize every choice for our citizens first. I think that's what the public expects of us in this country.

Consistent with that, we have had conversations with companies urging them, whenever possible, to make sure that adequate sup-

plies were slotted for U.S. needs and making the most passionate, if not the most convincing case that we could to them, about why we thought that was important. I think that is our position.

Mr. SHAYS. Now does FDA know precisely the amount that is exported? I'm not asking you to disclose that, but I want to know if you know precisely the amounts.

Dr. FRIEDMAN. I think we do know, that we do have, at least when there is sampling done—every month or 3 months or 6 months—we do know at that snapshot how much is being exported.

Mr. SHAYS. But you don't know for a year how much was exported?

Dr. FRIEDMAN. We can accumulate that information.

Mr. SHAYS. You haven't done it?

Dr. FRIEDMAN. I'm sorry, sir?

Mr. SHAYS. That has not been done?

Dr. FRIEDMAN. Yes—I'm sorry. What I'm told is that we have gotten that number. We have the total amount that is produced. The amount that's exported versus the amount that's used domestically was given to us by the industry.

Mr. SHAYS. OK. I would make this request. I would like you to determine how much is exported by each company, and with the company overseas how much they actually send back of what was sent to them, for the record. And I'll just close by asking the others to respond to the issue of export.

[The information referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 02 1998

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
Committee on Government Reform and Oversight
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

This letter is in response to questions you asked during the hearing held on May 7, 1998, Public Health 2000: Immune Globulin Shortages: Causes and Cures concerning exports of Immune Globulin Intravenous (Human) (IGIV).

You asked Dr. Michael A. Friedman, Lead Deputy Commissioner, Food and Drug Administration (FDA or Agency), to provide for the record the following: 1) the amount of IGIV exported by each company; and, 2) with respect to the IGIV produced overseas in facilities licensed by FDA, an estimate of how much United States derived plasma is sent to those facilities for processing into IGIV compared to the amount of IGIV returned to the United States.

FDA analyzed data received prior to the hearing on IGIV distribution and exports from product manufacturers. FDA requested an update of that data from the International Plasma Products Industry Association (IPPIA) on May 14 to provide a more current response to your questions. IPPIA provided data to FDA in response to that request. According to IPPIA, the IGIV distribution data provided to FDA was obtained from the Georgetown Economic Services which collects such data. The data is summarized below. It should be emphasized that FDA has not independently verified the data provided to FDA either by the individual companies or IPPIA.

COMPANY	IGIV MANUFACTURED (kg)	IGIV EXPORTED (kg)	IGIV EXPORTED % of MFR'S PRODUCTION
ALPHA			
1996	2,507	97	3.87%
1997	2,538	176	6.93%
1998(FORECAST)	2,813	75	2.67%

COMPANY	IGIV MANUFACTURED (kg)	IGIV EXPORTED (kg)	IGIV EXPORTED % of MFR'S PRODUCTION
BAXTER			
1996	3,036	440	14.49%
1997	2,847	541	19.00%
1998(FORECAST)	3,354	503	15.00%
BAYER			
1996	5,665	1,718	30.33%
1997	6,880	1,920	27.91%
1998(FORECAST)	4,112	1,887	45.89%
CENTEON			
1996	2,579	110	4.27%
1997	758	26	3.43%
1998(FORECAST)	2,772	103	3.72%

The American Red Cross (ARC) does not manufacture IGIV. ARC supplies the plasma which is used as a starting material by other manufacturers who manufacture IGIV. According to information provided to FDA by ARC, 80 percent of the plasma that ARC collects and releases for fractionation is used to manufacture IGIV under contract by Baxter. ARC indicated that all of the manufactured IGIV, using 80 percent of ARC plasma, is distributed in the United States by Baxter.

The remaining 20 percent of the plasma collected by ARC is shipped to the Swiss Red Cross (SRC) who also manufactures IGIV for ARC under contract. According to information provided to FDA, after manufacturing IGIV from the ARC plasma, SRC historically has shipped 10 - 30 percent of the manufactured IGIV to countries other than the United States. SRC currently ships greater than 90 percent of the IGIV manufactured with ARC plasma to Novartis Pharma A.G., a distributor. Novartis distributes 100 percent of the IGIV received from SRC in the United States. This information was confirmed by the statement made by Dr. Deborah Dunsire, Vice President of the Oncology Business Unit, Novartis Pharma A.G., at the Public Health Service Advisory Committee on Blood Safety and Availability on April 28, 1998.

The following table is FDA's calculation of IGIV exported by each company expressed as a percent of total IGIV distributed in the United States by all of the companies. Total

United States distribution was reported to FDA under 21 CFR § 600.81 as 16,107 kg in 1996 and 14,225 kg in 1997.

COMPANY	1996	1997
ALPHA	0.6%	1.2%
BAXTER	2.7%	3.8%
BAYER	10.6%	13.5%
CENTEON	6.8%	0.2%
SWISS RED CROSS		2.3%

This letter contains confidential commercial information not releasable to the public under FDA's Freedom of Information regulations. We ask, therefore, that the Subcommittee not publish, or otherwise make public, any information contained in the enclosed documents. We would, of course, be glad to discuss with the Subcommittee staff the confidentiality of any specific information.

We hope this information is helpful.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: The Honorable Dan Burton
Chairman, Committee on Government
Reform and Oversight

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
and Oversight

The Honorable Edolphus Towns
Ranking Minority Member
Subcommittee on Human Resources
Committee on Government Reform
and Oversight

The Honorable Vince Snowbarger
Member, Subcommittee on Human Resources
Committee on Government Reform
and Oversight

Dr. SATCHER. Well, I'm going to respond to the way you asked it, and you said, "How concerned should you be that we're exporting products when there is a shortage in this country, and we have information that there's not a shortage in the countries to which it is being exported?" I think you should be greatly concerned. I think the bigger question is, What should you do about it and how should you do it? And I think that gets into some more complex issues in terms of free enterprise, the global market, and how we're going to deal with it. And I think we do need to discuss that and make some decisions.

Mr. SHAYS. I've decided that we're not going to resolve all the questions today, so—[laughter]—but, you know, Dr. Satcher, all of you have a nice way of helping someone like me understand how I can frame it and understand the issue. So I'm appreciative to all of you in that regard.

Dr. Ostroff.

Dr. OSTROFF. I would just mention briefly, at least to our knowledge, the intramuscular immune globulin is not exported overseas. It's all stayed domestically, so that's not an issue for the IGIM. And as far as the other comments, I would be in total agreement with the comments of Dr. Satcher and Dr. Friedman.

Mr. SHAYS. Thank you. Ms. Steinhardt?

Ms. STEINHARDT. Well, just reacting to this, sort of in a logical way, if we're talking about triaging and looking at off-label uses and less essential uses in the United States, I'm not sure why you wouldn't include the global consumer as well. It just seems to make sense if you're looking at essential versus less essential, or the most essential versus less essential, that you would look at all of the consumers of that product, regardless of what country they were in.

Mr. SHAYS. Well, what you're addressing then would be if there were non-essential uses overseas, but I'm saying even if there were essential uses overseas. But——

Ms. STEINHARDT. But especially if there were non-essential uses overseas.

Mr. TOWNS. Mr. Chairman, will you yield?

Mr. SHAYS. Yes, definitely.

Mr. TOWNS. I think we really have to be careful with this issue. You know the world is a small place, and it could be us today and them tomorrow, them today and us—you know—I mean—and trade barriers. We really have to be careful. I think that—and I appreciate the comments that are being made—but I must admit that this is a very difficult one.

I know there are a lot of questions here that would have to be asked and answered, because the point is that you wouldn't want someone else to have something that we need and could not get it, but I'm certain that other countries feel the same way. And being that the world is so small, I think that we really have to be careful on this issue, and I think it needs to be thought out very carefully because I think we talk about it in terms of trade barriers and all that kind of stuff that we get into, and that's a real, real question. Inasmuch as I think that I can understand, in terms of your commitment to people in this country, but, still, maybe tomorrow it

might be another thing. I mean, so we need to be careful as we move with this.

Mr. SHAYS. I agree with the gentleman. I'm sure that Mr. Snowbarger does as well. I just want to say that we have to raise all of these questions.

Mr. TOWNS. Sure.

Mr. SHAYS. And because I happen to agree with the gentleman, I didn't want to get into the details of it. But I clearly believe that if there are shortages in this country and the blood is being donated by Americans, and being sent overseas, that has to be addressed. It has to be addressed.

Is there any last comment that each of you would like to make—a short one, because we have 12 minutes to vote.

Dr. SATCHER. I just want to thank you for the opportunity. It is a very important issue, and I think we're making progress as we're having these kinds of discussions.

Mr. SHAYS. Thank you, Dr. Satcher.

Dr. FRIEDMAN. I would only briefly say that I think in the past this committee's interest has been on how we manage the blood supply. Certain suggestions, recommendations, urgings have come from this committee. I hope that you've seen that we've taken seriously those, that we've followed through, and we do so to best serve the public health. As always, I appreciate the thoughtful way in which the committee has approached these difficult complex matters, not from a blameful perspective, but in an analytic and critical perspective. We appreciate that very much, sir.

Mr. SHAYS. Thank you, Dr. Friedman, for your kind words, as well as Dr. Satcher's.

Dr. OSTROFF. And I would just say, speaking for CDC, we are very appreciative of the continued interest of the committee on these issues, and we are certainly looking forward to the day that these issues can be resolved.

Mr. SHAYS. Thank you.

Ms. STEINHARDT. And as always, Mr. Chairman, we appreciate the opportunity to work with you.

Mr. SHAYS. Sorry; I wasn't asking for compliments on this. [Laughter.]

Let me say this to you. All four of you have honored our committee and have been very helpful with your information. And we're going to run off, so we're not going to say good-bye, but we do have a vote. Thank you.

Dr. FRIEDMAN. Thank you.

Mr. SHAYS. We're going to adjourn and we'll be in recess and be back in 15 minutes and start with the next panel. Thank you.

[Recess.]

Mr. SHAYS. I call this hearing to order and invite our guests to sit down. Our second panel is Donna Hobson, president, Immune Deficiency Foundation of Nebraska; Robert Kobayashi-hold on a sec, I'm going to get it right. [Laughter.]

Kobayashi? Close enough?

Dr. KOBAYASHI. Exactly perfect.

Mr. SHAYS. Thank you, sir, and I'm not going to say it again. Let's see, Dr. Kobayashi, Immunologist, Omaha, NE; and Dr. Douglas Scheckelhoff, excuse me, is it doctor?

Mr. SCHECKELHOFF. Mister.

Mr. SHAYS. Yes; director of pharmacy, Children's National Medical Center, Washington, DC. And I will invite you all to stand, and we will swear you in.

[Witnesses sworn.]

Mr. SHAYS. Thank you. For the record, all three have responded in the affirmative.

It's very nice to have you here. I'm sorry you had to wait so long, but it was a very helpful panel and we wanted to pursue the information.

So, you all have 5 minutes, and then we roll the clock over another 5 minutes. We need to have you stop before that second red light comes back on again.

And we'll do it in the order I called you. So, Mrs. Hobson? Thank you.

STATEMENTS OF DONNA HOBSON, PRESIDENT, IMMUNE DEFICIENCY FOUNDATION OF NEBRASKA; ROGER KOBAYASHI, M.D., IMMUNOLOGIST, OMAHA, NE; AND DOUGLAS SCHECKELHOFF, DIRECTOR OF PHARMACY, CHILDREN'S NATIONAL MEDICAL CENTER, WASHINGTON, DC

Ms. HOBSON. Good afternoon. I would like to thank this subcommittee for inviting me to participate in this hearing on the nationwide shortage of intravenous immune globulin. My name is Donna Hobson, and I am president of the Nebraska chapter of the Immune Deficiency Foundation. I am also a primary immune deficient patient.

I would like to share with you today my personal story, to allow you to understand how the current nationwide shortage of IVIG has affected my life, and that of many thousands of other immune deficient patients. For most of my adult life, I could not easily recover from common infections. It would seem odd to those who knew me well that a cold, flu, or sinus infection would often linger for weeks and months. However, in 1987, my health took a dramatic turn for the worse. A series of overwhelming infections, including bronchitis, otitis, and sinusitis led to pneumonia and staph infections. I was hospitalized, often placed in isolation, and given intravenous antibiotics.

I continued to self-administer intravenous antibiotics for 1½ years, and still the high fevers and infections persisted. I was sent to several doctors and hospitalized repeatedly. One year, my hospital bill was $50,000, and 38 out of 44 days, I had visited my doctor in his office. Every day, I was losing ground, until in 1989, I was referred to an immunologist, Dr. Kobayashi, who diagnosed me with Common Variable Immunodeficiency. This is a primary immunodeficiency which often has an adult onset. Immediately after my diagnosis, I was placed on intravenous immune globulin replacement therapy. IVIG replaces my incomplete immune system, and allows me to fight off the infection to which I would have previously succumbed, and which have the potential to be life-threatening.

For the past 9 years, I have received IVIG on a regular basis, varying from 2 to 3 weeks, and I am very happy to report I have not had one hospitalization since beginning this therapy. One of my

physicians stated that he believed that I was going to die, and believed without the IVIG I would have died.

Mine is a typical story for patients with primary immunodeficiency disease. Over 50 percent of all patients with primary immunodeficiency disease are infants and children. Early detection and IVIG treatment in these children prevent the occurrence of debilitating infections such as pneumonia, causing lifelong chronic illness and disability.

The Nebraska chapter was founded by me and my husband in the hope that anyone who receives a diagnosis of primary immunodeficiency will know that they are not alone. We have also worked hard to educate primary care physicians, nurses, and other medical personnel to properly diagnose and treat these patients.

This is why I am here before you today. I want to share this miracle that the therapy has brought into my life and tell you the anxiety and health consequences that patients like myself are suffering as a result of the shortage.

The Immune Deficiency Foundation recently conducted a survey of physicians and patients to learn about their experience with the shortage. The results of the survey are astounding: 87 percent of the physicians responding report that they have had difficulty obtaining product; 45 percent of patients report adverse health effects, which include more infections, pneumonia, bronchitis, lung infections, as well as stress and anxiety. I would like to share some of the comments made by patients on the survey form. One mother writes, "I find this thoroughly unacceptable that my child has to go on a priority needs list to get medication so that he may live a normal, 10-year-old's life." Another writes, "My 13-year-old daughter has missed a lot of school, had more frequent and severe infections, and is in more joint pain. She is requiring more antibiotics and more pain medication than she has ever needed." Back home in Nebraska, I know of a young mother of three who literally spends hours every day on the phone trying to obtain the product. She worries constantly about who will care for her family if she became ill and had to be hospitalized.

I have just become aware today of a situation in Florida where a gamma lottery is being held, and I have a poem here from an 11-year-old that was written. "Need gamma? Take a chance in the lottery. Did you hear it's a lottery, who will live, who will die. I beg, I cry, choose me, choose me. Hurray, I've won. Another chance, another time. So sorry you've lost. You'll get sick. You may die. Did you hear? It's a lottery, a chance to live, a chance to die." That was written by an 11-year-old, Amy, from Florida.

My husband is vice president of a regional pharmacy chain. My insurance company covers the cost of my therapy, and still I'm on pins and needles as the date of my next infusion rolls around. I go day to day wondering if the gamma will come in. I've had to rely on my physician to share his supply, because my usual source has not come through. But still, my biggest fear is that one day there will be none available, and I will have gone long enough without my infusion that I will succumb to some type of infection that will place me back in the hospital, or worse.

I would like to thank this committee and the Health and Human Services Committee for the attention that you have brought to this

critical matter. I would recommend that a strategy be developed immediately that ensures that the patients who depend on this life-saving therapy will be assured that their IVIG will be available. Thank you.

Mr. SHAYS. Thank you very much.

Doctor.

Dr. KOBAYASHI. Mr. Chairman, my name means "woods" in Japanese.

Mr. SHAYS. Woods?

Dr. KOBAYASHI. Woods. My ancestors picked the name Kobayashi just to twist tongues. [Laughter.]

Good morning, Representative Shays, members of the subcommittee, and guests. Thank you for inviting me to describe in human terms how this shortage has affected our patients. In the next 5 minutes, I'll tell you how those of us in the medical trenches have been affected, and what we have done during this period of grave IVIG shortage.

My name is Roger Kobayashi, and I'm a practicing allergist/immunologist from Omaha, NE, and a clinical professor of pediatrics at the UCLA School of Medicine in Los Angeles. In the clinics where patients with immunodeficiency are seen, there continues to be a worrisome shortage of IVIG. One of my colleagues, Dr. David Rosen, a pediatric hematologist from Wichita, KS, could not obtain IVIG for one of our mutual patients, Troy Ayers, a college freshman with hyper-IgM syndrome, which is generally fatal unless IVIG is available. He used to receive his treatments in Dr. Rosen's office; however, I recently received a letter from Troy's mother, and she relates,

> The blood specialist doctor was unable to receive supplies, and therefore Troy was infused in the hospital. However, the hospital did not have enough, and called three other hospitals in Wichita, and they were all out. Troy's doctor in Wichita has put him on the priority list, but it still worries me that one of these days, he'll go in and there won't be any. This is a life-and-death deal for Troy, because he does not make any antibodies.

This story is repeated over and over again in the Midwest and elsewhere.

In a survey done by the Immune Deficiency Foundation, and reported at the HHS meeting, blood safety meeting on April 27, 87 percent of doctors taking care of children and adults with immune deficiency reported difficulty with obtaining IVIG in the past 6 months. More significantly, of those doctors taking care of the most patients, that is, following 25 or more individuals, 93 percent reported difficulty in obtaining IVIG.

I would also like to point out that the Alpha One Foundation, headed by Dr. Walsh also reports with alpha one protease inhibitor that a similar and parallel deficiency occurs.

Let me tell you about our experience. I have been practicing immunologist/allergist in Omaha for the past 7 years, after leaving full-time academics, and have begun to serve as regional caregiver for patients requiring immune globulin. I am privileged to take care of approximately 75 to 80 children and adults receiving IVIG within a five-State area, and infuse approximately 30 patients in our offices. I've been able to receive IVIG product directly from some of the manufacturers. I am on their highest priority list for

immune globulin. Yet, in the fall of last year and continuing to the present time, I have experienced significant shortages. From day to day, our group has worried whether we would have enough IVIG to infuse our patients.

After considerable consternation, a letter dated February 21, 1998, was sent to our patients. Several points were made. No. 1, the situation had become critical. No. 2, we could not guarantee that we had enough IVIG for our patients. No. 3, we had to ration, switch products, increase intervals, and decrease the amount of IVIG given. In addition, when new immune-deficiency patients were referred to me and IVIG was required, I was quite concerned whether we'd be able to secure products for these patients.

Let me relate another story about one of the patients that I had. One of my patients suffering from hypogammaglobinemia and severe lung disease, which required him to be on continuous oxygen supplementation, was recently admitted to a major Omaha hospital with acute bacterial pneumonia. In addition to antibiotics, he required IVIG, and the hospital could not get the brand that he needed. Since he had several severe reactions to other IVIG brands, the hospital called us to see if we had the brand he used. We volunteered some from our supplies. One month later, this hospital has still not been able to replace what they've borrowed from us.

What does it mean when 87 percent of doctors recently surveyed have difficulty in obtaining IVIG? What does it mean when 45 percent of responding physicians report negative health impact on the patients as a result of these shortages? What does it mean when 45 percent of the patients responding report adverse health effects? What does it mean when I, as a physician, find it difficult to ration IVIG because I am personally involved in caring for these patients on a close and intimate basis, worrying where and whether supplies will be available to meet the needs of these patients?

Chairman Shays, Members, this is not a good situation. Let me finish up by saying, let me again say that it is the uncertainty of not knowing whether IVIG will be available when you come in for monthly infusions that causes fear and anxiety among patients, and worry among doctors. As stated in my letter to our patients, our group has begun rationing products, and the personal turmoil of having to make decisions which might compromise the best care I can give to my patients has been a disturbing burden.

In ending, I would like to emphasize that even in a small State like Nebraska, we are feeling the effects of shortage similar to our brethren in Texas, California, New Jersey, Florida, and elsewhere. Thank you.

[The prepared statement of Dr. Kobayashi follows:]

Good morning, Representative Shays, members of the Subcommittee and guests. Thank you for inviting me to describe in human terms how this shortage has affected our patients. In the next five minutes, I will tell you about how those of us in the "medical trenches" have been affected and what we have done during this period of grave IVIG shortage.

My name is Roger Kobayashi and I am a practicing allergist immunologist from Omaha, Nebraska and a Clinical Professor of Pediatrics at the UCLA School of Medicine in Los Angeles. In the clinics where patients with immunodeficiency are seen, there continues to be a worrisome shortage of IVIG. One of my colleagues, Dr. David Rosen, a pediatric hematologist from Wichita, KS could not obtain IVIG for one of our mutual patients, Troy Ayres, a college freshman with hyper-IgM syndrome, which is generally fatal unless IVIG is available. He used to receive his treatments in Dr. Rosen's office however, I recently received a letter from Troy's mother and she relates: "The blood specialist doctor (Dr. Rosen) was unable to receive supplies and therefore, Troy was infused at the hospital. However, the hospital did not have enough and called three (3) other hospitals in Wichita and they were all out. Troy's doctor in Wichita has put him on the priority list, but it still worries me one of these times, he will go in and there won't be any. This is a life and death situation for Troy because he does not make any antibodies." This story is repeated over and over again in the Midwest and elsewhere.

In a survey done by the Immune Deficiency Foundation and reported at the HHS, Blood Safety meeting on April 27, 87% of doctors taking care of children and adults with immune deficiency reported difficulty obtaining IVIG in the past (6) months. More significantly, of those doctors taking care of the most patients, that is following 25 or more individuals, 93.4% reported difficulty in obtaining IVIG.

Let me tell you about our experience. I have been a practicing immunologist allergist in Omaha for the past seven- (7) years after leaving full-time academics and have begun to serve as a regional caregiver for patients requiring immune globulin. I am privileged to take care of approximately 75 to 80 children and adults receiving IVIG within a five- (5) state area and infuse approximately 30 patients in our Omaha offices. I have been able to receive IVIG product directly from some of the manufacturers. I am on their highest priority list for immune globulin. Yet, in the fall of last year and continuing to the present time, I have experienced significant shortages where, from day-to-day, our group has been worried whether we would have enough IVIG to infuse our patients. After considerable consternation, a letter, dated February 21, 1998 (copy provided to the Committee) was sent to our patients. Several points were made.

1. **The situation had become critical**
2. **We could not guarantee that we had enough IVIG for our patients.**
3. **We had to ration, switch products, increase intervals or decrease the amount of IVIG given.**

In addition, when new immune deficient patients were referred to me, and IVIG was required, I was quite concerned whether we would be able to secure product for these new patients.

Similarly, hospitals in Omaha and Lincoln have often been unable to obtain supplies for patients and frequently, those patients I follow who are receiving IVIG at hospitals or associated clinics at distant sites have also great difficulty in obtaining supplies. One of my patients suffering from hypogammaglobulinemia and severe lung disease, which requires him to be on continuous oxygen supplementation, was recently admitted to a major Omaha hospital with acute bacterial pneumonia. In addition to antibiotics, he required IVIG and the hospital could not get the brand he uses. Since he had severe reactions to other IVIG brands, the hospital called us to see if we had the brand that he used. We volunteered some from our supplies. One month later, the hospital still has not been able to replace what they borrowed from us. Like other hospitals throughout the country, hospitals in our area have searched desperately for IVIG from their contractual sources as well as from secondary wholesalers.

Mr. Ted Tianello, Head of Pharmacy Administration at Omaha Methodist Hospital, a major university affiliated institution tells me that they are constantly worried about IVIG shortages. They have assigned one (1) pharmacist whose sole responsibility at this time, is to call around the country to see if IVIG is available. He also told me that they called their friends on the East Coast and Florida to see if any was available. I found it admirable and compelling that the pharmacy department was doing all within their power to find enough IVIG for patients. Mrs. Linda Kuhlenengle, whose children I take care of, is Chief Pharmacist and purchaser for Bergan-Mercy Hospital, the busiest private hospital in Omaha. She often cannot get IVIG for their cancer specialists who require it for their patients. She and others spend countless hours calling their contacts to try and obtain product. She is in the unenviable position of being on the receiving end of the anger and frustration from the doctors because the pharmacy is unable to secure IVIG.

What does it mean when 87% of doctors recently surveyed have difficulty in obtaining IVIG? What does it mean when 45% of responding physicians report negative health impact on their patients as a result of these shortages? What does it mean when 45% of patients responding report adverse health effects? What does it mean when I, as a physician, find it difficult to ration IVIG because I am personally involved in caring for these patients on a close and intimate basis, worrying where and whether adequate supplies will be available to meet the needs of these patients. Chairman Shay, Members, it means that this is not a good situation. Soon you will be hearing from Donna Hobson, the President of the Nebraska Chapter of the Immune Deficiency Foundation and a patient of mine with common variable immunodeficiency. She will tell you about the ongoing fear and anxiety worrying about whether IVIG is available.

The Chairman is acutely aware of the current shortages of IVIG. The Chairman is acutely aware of the concerns of these patients because of these shortages. The Chairman is aware of the NIH Consensus Conference recommendations on the use of IVIG. The Chairman is aware of the excellent reviews published by Dr. E. Richard Stiehm, of UCLA, and Drs. Buckley and Schiff, of Duke University, regarding the recommended uses of IVIG. The Chairman is aware of the recommendation made by the Advisory Committee on Blood Safety and Availability. The Chairman is aware of the recommendations of the FDA and the IPPIA, ably represented by Mr. Jan Bult. Let me say that I endorse and am encouraged by the 14 recommendations thoughtfully outlined by the Advisory Committee on Blood Safety and Availability headed by Drs. Arthur Caplan and Stephen Nightingale. I especially support short-term recommendation #2, which reads as follows:

> *The Department of Health and Human Services should explore, in collaboration with industry, health care providers, and appropriate consumer groups, methods to optimize and standardize allocation of available products in an equitable manner, including management of emergency supplies and programs that distribute products directly from manufacturers to registered consumers.*

This short-term recommendation has also been set forth by Mr. Jan Bult of IPPIA. I strongly urge that supplies be made available to patients most in need and who would be seriously harmed if product were unavailable. Similarly, I strongly support recommendation #5 from the long-term category, which states:

> *The National Institutes of Health and industry should support the continued evaluation of the use and appropriate dose of intravenous immunoglobulins for indications where its benefit requires further-delineation, and the results of these evaluations should be rapidly disseminated to the public.*

We need to have valid information regarding use in diseases where IVIG may be of benefit.

In closing, Mr. Chairman, let me again state that it is the uncertainty of not knowing whether IVIG will be available when you come in for monthly infusions that causes fear and anxiety among patients and worry among doctors. As stated in my letter to the patients, our group has begun rationing product and the personal turmoil of having to make decisions, which might compromise the best care, I can give my patients has been a disturbing burden.

In ending, I would emphasize that even in a small state like Nebraska, we are feeling the effects of the shortage similar to our brethren in Texas, California, New Jersey, Florida and elsewhere. Thank you.

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February 21, 1998

Re: Severe Shortage of IV Gammaglobulin

Dear Patients:

For the past year, there has been a nationwide shortage of IVIG where hospitals and clinics were having great difficulty securing product. Over the past 2 months, the situation has become critical and our office, which up until this juncture has been able to receive sufficient quantities of IVIG, now cannot guarantee that we will have enough for all our patients. We have been contacting the manufacturers directly and until now, they were able to allocate IVIG to us from their emergency inventories. These are becoming exhausted. The manufacturers are trying their best to replenish their stocks, however this will take some time; the shortage is worldwide.

The *Immune Deficiency Foundation* is working hard to help in any way they can both regionally [Donna Hobson] and nationally. You should contact them to find out the current status of this nationwide shortage.

In the meanwhile, our group will do everything we can to secure enough supplies for all of our patients. This may mean we might have to switch some of you to different brands [if we can get others], temporarily decrease the amount given [e.g. instead of 25 grams we may give you 20 grams so that we might have some IVIG for another patient], or spread out the interval so that the supplies last longer [e.g. 4 weeks to 6 weeks].

If you have any questions, please do not hesitate to call me or if you have questions where the *Immune Deficiency Foundation* may help, please contact the national headquarters or Donna Hobson in Omaha.

Sincerely yours,

Roger H. Kobayashi, M.D.
Clinical Professor of Pediatrics
UCLA School of Medicine
Former Director of Immunology UNMC

RHK/lg

cc. Lincoln Office, Immune Deficiency Foundation

Board Certified in Adult and Pediatric Asthma and Allergy

Members of the American Academy of Allergy and Immunology

Mr. SHAYS. Doctor, thank you very much.

Doctor.

Mr. SCHECKELHOFF. Good afternoon, Mr. Chairman, members of the subcommittee, and guests. My name is Douglas Scheckelhoff, and I'm the director of pharmacy at the Children's National Medical Center here in Washington, DC. I truly appreciate the opportunity to come here today and to have the opportunity to address this group. This is a very important issue.

It's the pharmacy's responsibility at our hospital to purchase, prepare, and dispense immune globulin products. The normal process would be that our buying group would submit a request for quotations from the different manufacturers. They would submit a bid or price, and then they would establish a contract with that company, at a given price, the best price, for us to use. We would then purchase the product at that price, and obtain it through normal distribution channels, stock the product, and dispense it pursuant to a physician's order.

We have witnessed many recalls and withdrawals over recent years. The biggest impact this has had for us has been with albumin, decreasing supply and raising the price. In 1997, we saw that those recalls and withdrawals started to expand to other blood products, most notably immune globulins. We started to feel the effect of those shortages in the fall of 1997. It hit us most significantly in November of last year.

So as we tried our usual suppliers, contacted manufacturers and distributors, we found that we were unable to get the product and we had to go to alternate sources. One other source that we found occasionally had the product was a group of companies or distributors that are probably best described as specialty distributors. All they sell are blood products: albumin, immune globulins, Factor 8, Factor 9, typically, and maybe some of the other related products, but that's the main part of their market.

They have brand-name products from U.S.-based manufacturers, but they sell it at a much higher price than what we would normally pay under our contractual arrangements. We typically pay our normal contract price of between $20 and $25 per gram of immune globulin, and we have contracts with several different manufacturers. We've been forced to pay between $40 and $50 per gram routinely in the last 6 months from these varying sources, just because we had to get the product. We've had situations where our supply was severely low, and we've had to pay as much as $85 per gram, just to get in the product so that we were able to meet patient needs.

These specialty distributors also will occasionally bundle products, like IVIG, for example. They will have immune globulin to sell, but in order to buy it you must also buy albumin from them at a premium price to get the IVIG, even if you don't have a need for the albumin.

The usual dose that we have for patients depends on the patient's weight and the indication. It can be in the range of 10 to 20 grams for a small patient for given indications, and can range to up over 100 grams for a larger patient with different patient needs. On a good week, we'll have 300 grams, potentially, on the shelf, and we'll be able to accommodate multiple patients who may

have a need. We do have times where our supply dwindles down below 100 grams, to 50 or 75 grams, and we spend a great deal of time in making many, many phone calls to try to obtain product.

We have a pharmacist and a technician who both spend a significant amount of time obtaining product, but also controlling the supply that we have. We have a pharmacist who's available 24 hours a day, who screens all of the orders, to work with physicians to make sure that the orders are appropriate, the doses are appropriate, and that we have supplies before a patient is told to come to the hospital to receive their product.

We have had some luck recently with the emergency supply programs that we've heard described earlier today. In those programs we contact the company, we tell them about our need, we give them the name of the physician and the indication that we're using for, and they will ship us the amount of product needed for that one dose or that one course of therapy. It has improved the situation over the last 30 to 45 days, in that they have had the product and they have sold it to us at our contracted price. It is a time-consuming process, and it's not a long-term practical solution, but it has improved the situation.

We've been fortunate in that we have not had to adversely affect patient care in a significant way, but it has taken an investment of time, energy, and money to pay these higher prices for this product, and a lot of time trying to get something that is very hard to find.

We look forward to the subcommittee's deliberations, and hopefully coming to some resolution with these problems. Again, I thank you for the opportunity to address this group.

[The prepared statement of Mr. Scheckelhoff follows:]

Good morning, Mr. Chairman, members of the Subcommittee, and guests. My name is Douglas Scheckelhoff. I am the Director of Pharmacy at the Children's National Medical Center here in Washington DC. I have been a pharmacist for 15 years and have been at Children's since February of 1997. I appreciate the opportunity to come before this Subcommittee and testify on the implications of the intravenous immune globulin shortage.

Our pharmacy is responsible for the purchase, preparation and dispensing of intravenous immune globulin (IVIG) products for the patients in our hospital. The normal process is that our buying group would bid out the product, establish the best possible contract price, we would buy it though the established distributor as needed, and we would prepare the product pursuant to a physician's order.

There have been many recalls of blood products and resulting shortages over the last few years, but they have primarily been with albumin. This has often resulted in higher prices and difficulty in obtaining an adequate supply.

In 1997, we began seeing a larger number of recalls for blood products, which included not only albumin but other blood products as well. We specifically began experiencing supply problems with immune globulin in the fall of last year. Our normal contracted manufacturers were not able to consistently supply product, which put us in the situation of trying to find product with alternate sources.

A secondary source of product that we have had to turn to when the normal distribution channels are exhausted is a group of companies that act as "specialty distributors". These companies typically only sell blood products like albumin, immune globulins, or antihemophilic factors and frequently are the only place to turn when the manufacturers have no product. There appear to be more and more of these specialty distributors that have evolved as the blood product shortage has grown. These distributors have brand name products - usually on a sporadic basis - that they sell at significantly higher prices than those we pay under contract.

Our usual contract price with a manufacturer is $20 to $25 per gram of immune globulin, but since the shortage we commonly pay $40 to $50 per gram from specialty distributors. When supply was extremely short, we have had situations where we have had to pay as much as $85 per gram. This is after 12 to 15 phone calls with manufacturers, wholesalers, and any other supplier that would otherwise stock the product. We simply have no other options. We had to have a supply of this lifesaving product that has few therapeutic alternatives.

Sometimes these specialty distributors "bundle" other products to immune globulin purchases. For example, they will sell you the immune globulin, but you must also buy a certain quantity of their albumin at a higher than normal price

even though you may not have a need for it. We've have heard of prices for immune globulins from the specialty distributors as high as $115 per gram.

We now spend 6 to 8 hours per week on average of pharmacist and technician time trying to obtain immune globulins and control the very limited stock that we have. Our doses are typically anywhere from a low of about 20 grams to well over 100 grams, usually based on the weight of the patient. On a good week we have 200 or 300 grams of product and could accommodate 3 or 4 patient's doses. When our supply drops below 100 grams our situation becomes critical and our staff spend countless hours trying to obtain product, reluctantly paying high prices to avoid putting the patient at risk.

We have had some luck in the last few weeks with some of the manufacturers. One in particular, has been able to supply product on an emergency basis, one dose at a time. So when we have a need, we contact the company, give the prescribers name and indication for use, and they ship us enough for that one dose and it is at our contracted price. This buys us time until the next dose is needed.

Through an investement of time, energy, and money, we have been fortunate that we have not adversely affected patient care up to this point. When our supply is low, we notify all our physicians so that they can consider delaying elective use of immune globulins until we again have product. We have also

been in the situation where we have rescheduled outpatient appointments to a time when we know we have adequate supply. They can also consider therapeutic alternatives, which in a few cases may exist. When we do get an order, our pharmacist contacts the prescriber, and they work through the most appropriate dose that will be therapeutically effective while allowing us to conserve our limited supply.

We look forward to the subcommittee developing solutions to this public health problem. Thank you for the opportunity to address this distinguished group.

Mr. SHAYS. I thank all of you for your testimony. I find this an absolutely fascinating issue. The implications are fascinating, and I'm going to make some analogies and try to get your response.

But first, Mrs. Hobson, in your judgment, is it as difficult now as it was? When was the worst point backup? Dr. Friedman believes, based on calls to FDA, that the situation is getting better. Is the situation getting better?

Ms. HOBSON. No. We're not finding it any better. I spoke with a young mother the other day, Tuesday, I believe it was. And her physician had told her that she had the product for February, March, and April, but there was no product for May. And she was in tears. So, definitely, from the mothers that I have talked with and the mothers of children, they find it's not getting better.

Mr. SHAYS. Doctor, is your sense that it's getting better?

Dr. KOBAYASHI. I believe that the shortage is still significant. As I mentioned, we are on the highest priority list. The University of Nebraska Medical Center is also on the highest priority list. And we are having difficulty getting it. So if we have difficulty getting it, I suspect others would be having problems, as well.

Mr. SHAYS. Mr. Scheckelhoff?

Mr. SCHECKELHOFF. I guess my sense is that it's such a sporadic problem. We haven't had a great deal of difficulty using the emergency——

Mr. SHAYS. If you'd just put the mic a little closer. Yes.

Mr. SCHECKELHOFF. We've used the emergency supply program in the last 3 to 4 weeks, and have been able to get supplies, but that could change in a week and next week we could have great difficulty. Since it's such a sporadic thing, but I really don't have a sense that it's dramatically improving, although we have had better luck in recent weeks.

Mr. SHAYS. We have a very interesting panel, because we have, basically, someone who needs immune globulin, we have a doctor who treats, and we have a pharmacist who distributes directly to the patient. So you all have a little different perspective, but you all are very close to this issue. The emergency supplies network—is the cost higher, or is it about the same?

Mr. SCHECKELHOFF. The product that we have obtained through that system has been at the contracted price, roughly $24 per gram.

Mr. SHAYS. OK. So it hasn't increased?

Mr. SCHECKELHOFF. If you get it from the manufacturer, through the emergency supply program.

Mr. SHAYS. Right. OK. And the emergency supply program comes from the manufacturer?

Mr. SCHECKELHOFF. Right.

Mr. SHAYS. OK. Dr. Kobayashi?

Dr. KOBAYASHI. I believe that the price has increased to us from the contractual basis. My concern is the amount of time we spend scrambling around trying to find product. We have patients coming in, and it is very disconcerting——

Mr. SHAYS. Doctor, we're going to get into that. I understand that that would be, obviously, a logical concern. I just want to understand. You had a contracted price which was below the pharmaceutical price—the price to the pharmacy?

Dr. KOBAYASHI. The price, the contractual price, has increased.

Mr. SHAYS. Has increased?

Dr. KOBAYASHI. Yes.

Mr. SHAYS. Has increased?

Dr. KOBAYASHI. Has increased.

Mr. SHAYS. But the hospitals were probably given some discount? I just want to get the perspective right?

Dr. KOBAYASHI. Yes.

Mr. SHAYS. So, in your case, the price has gone up from the contracted price; in the case of the pharmacy, the price has remained the same for emergency supplies. Mrs. Hobson, how do you find it?

Ms. HOBSON. Again, a patient that I visited with on Tuesday told me that since her last infusion—her last three infusions, her price of the gamma has tripled.

Mr. SHAYS. OK.

Ms. HOBSON. And she buys this through her physician.

Mr. SHAYS. And is it covered through the insurance?

Ms. HOBSON. Only a certain amount, and she said that she's going to have to pay the difference. Her insurance will not cover it.

Mr. SHAYS. Now, when we had the gasoline shortage—and it's amazing to think of that very weird moment in our lives—at least in New England, maybe not in other parts, but I remember getting up at 4:30 a.m., literally being in line. In the beginning, we didn't know how to deal with it, so you might get up there when the station ran out of gas. Eventually they started putting the sign up so many cars back. I remember making sure the tank was always full, and then you'd have extra tanks. And we realized that part of the shortage was just clearly the fear and the hoarding of those who consumed it.

Is it possible that—and no criticism if this were the case—I would be seeking to do this if I were someone who needed this? Is there a practice on the part of those who use immune globulins and other parts of the blood supply to buildup a supply, so that they don't have to go through the agony that the doctor's described?

Ms. HOBSON. I'm sorry, I didn't understand the question.

Mr. SHAYS. Yes. You know what? It was such a long question. [Laughter.]

I'm going to give you the short version. The short version of it is: are those who use immune globulins, are they trying to buildup supply, and could they in fact be contributing to the shortage because they're trying to stockpile, so that they don't have this——

Ms. HOBSON. The patients themselves?

Mr. SHAYS. Yes, the patients themselves.

Ms. HOBSON. No. Patients are going month-to-month, day-to-day, week-to-week.

Mr. SHAYS. You know of no patients that have been able to buildup an extra supply?

Ms. HOBSON. None that I know of, no.

Mr. SHAYS. Doctor?

Dr. KOBAYASHI. No, I think under the circumstances, that would not be possible.

Mr. SHAYS. Fascinating.

Mr. SCHECKELHOFF. Yes, I'm not aware of anybody who's doing that. I think it would be very difficult to do.

Mr. SHAYS. Mr. Towns, I'll go to you, and then come back.

Mr. TOWNS. Sure.

Mr. SHAYS. Thank you.

Mr. TOWNS. Mr. Chairman. I only have one question. I know it's going to be hard for you to believe.

Mr. SHAYS. I'll bet you don't have just one question.

Mr. TOWNS. Just one, 15 parts. [Laughter.]

If manufacturers—I guess Mrs. Hobson to you—if manufacturers decided to label their products with a warning label of CJD, instead of conducting product withdrawals, would this affect your willingness to use the product?

Ms. HOBSON. Since I've already taken product that's been recalled, and I know without the gamma that I'm at a great risk, I would take the product, because I don't believe that I could live without the gamma. So I would most definitely take the product.

Mr. TOWNS. I yield back, Mr. Chairman. Thank you so much.

Mr. SHAYS. Doctor, explain to me, if you miss a cycle—2, 3 weeks—do you then have to take twice as much the next time, or do you just take the same amount as soon as you can get it? Do you understand what I'm asking?

Dr. KOBAYASHI. You're asking if you miss a dose, whether you would have to take twice as much. I think it would depend on the patient. But there is a standard dose that is given to the patient, and that, together with the clinical status, determines how much and how often the patient is given IVIG.

Mr. SHAYS. So there's the standard dose, and the assumption I make is that if you have a gap, you are very vulnerable. But then if you are fortunate to now get what you need, you just start from there and you have some immunity for a period of time, and that lowers and then——

Dr. KOBAYASHI. Yes. Mr. Chairman, the IVIG is what we call passive immunity. This is that you're giving something which the body does not make, and the body metabolizes it, it uses it at a specific rate. So if you're not giving it on a regular basis, it will drop down to potentially problematic levels.

Mr. SHAYS. Right, but I want to get a general response to this question. I thought I had the answer, but now you make me wonder. If you don't have this protection do you have to take a lot more to buildup to a certain level, or is there truly a limit of what you can take and then from that point on you'll be OK for a period of a week or two.

Dr. KOBAYASHI. I'm not quite clear on the question that you're asking.

Mr. SHAYS. OK. Do you have to take an extra dose to catch up?

Dr. KOBAYASHI. You may have to get more.

Mr. SHAYS. OK, but not a lot—it's not one-for-one. If you have two units and 2 weeks later, to be simple, you have to take two more units, but you missed that 2-week period, you don't necessarily have to take four. And if you missed a whole month, you wouldn't necessarily have to take eight. In fact, you couldn't. It would be counterproductive. I'm seeing people agreeing behind you and they're not under oath. [Laughter.]

Dr. KOBAYASHI. Yes, that's correct. Yes.

Mr. SHAYS. OK. Mr. Scheckelhoff, would you just describe to me, the distributors who aren't the manufacturers who charge a premium price. You know my only analogy is thinking of wanting to see Michael Jordan, and the scalper has the ticket and you pay the price.

Mr. SCHECKELHOFF. Well, again, we have seen several of these distributors have appeared over the last several years, and it was initially, I think, to meet the need with albumin, because that was a very similar issue and has been for several years. And, again, we've received flyers and notification that these companies exist, and that they have IVIG, and so, again, it's supply and demand. They see a market, and they're able to obtain supply and sell it at a higher price.

Mr. SHAYS. But the inference I'm making is that the distributor—excuse me—the producer of the product, the manufacturer of the product, is going to charge you the stated rate. And I have a sense that there's an ethical aspect to that. I get the sense that if you're a middleman, middle person, here in this process, that you may attempt to get whatever price you can get. And I guess I want to get a sense of how serious is that in this whole issue.

Mr. SCHECKELHOFF. I think your assumption is correct. They charge what the market will bear.

Mr. SHAYS. Now I'm trying to understand how they get it. If patients who need it can't hoard it, how do distributors who aren't the manufacturers get it and make that extra buck?

Mr. SCHECKELHOFF. I have contacted these suppliers and asked them, basically, that question, and responses vary from distributor to distributor. Some of them get product directly from manufacturers. They have a monthly allocation. At one time, they would get 100,000 grams per month, and now they get only 5,000 or 10,000 grams. And that's probably a contractual basis. Others get it from other distributors, and where they get it, I don't know.

Mr. SHAYS. Well, we're going to ask the manufacturers, and it will be very important for them to describe the ethics of that process to me. I mean, I understand they have distributors. But it seems to me they can place requirements on their distributors.

What question would you have wanted me to ask that I didn't ask? What were you prepared to talk about if I had asked this question that I havent asked?

Oh, I'm sorry. You've been here the whole time? I apologize. [Laughter.]

Mr. SNOWBARGER. No problem. No, I wasn't here the whole time.

Mr. SHAYS. OK, great. I'm sorry. But I'll get to that question afterwards. I just wanted to make sure that I didn't let you go before we had covered what we needed to. So I'm really delighted to have you here.

Mr. SNOWBARGER. Well, Mr. Chairman, I just wanted to followup on the same line of questioning, because as I heard Mr. Scheckelhoff, I think, I can attribute it to you, talking about having to go to these other distributors. My analogy was I felt like I was looking at the commodities, you know. And you have speculators who are going out there buying supplies of commodities, and then hoping for a shortage so that they can come out and sell the prod-

uct at a higher price. I'm not frankly sure—I'm uncomfortable with that. I'm not very sure how I want to deal with that, though. I mean, is that too strong an analogy? Or is that what you sense when you're dealing with these folks?

Mr. SCHECKELHOFF. I think it's accurate. As we contact these companies and they say, you know, we're receiving 1,000 grams this afternoon. We can let you have 100 of that, they divvy it up, and they will only sell you a certain amount in limited quantities, and this is the price we're charging. And I think they know that, often, people don't have any other options.

Mr. SNOWBARGER. Do you have any sense that either they do, or there is an opportunity to do the hoarding that the chairman questioned earlier?

Mr. SCHECKELHOFF. I think it appears that they sell it when they get it, and don't stockpile. Especially if the market is such that they're able to get a price that is profitable for them, they sell it.

Mr. SNOWBARGER. But you're not aware of any mechanism in the distribution process that would prevent the kind of hoarding that we're talking about. I mean, it's nice to get, you know, $50 or whatever it was today, but if you can hang onto it and get $100 tomorrow. I guess that's my concern in terms of the speculation process, and, again, it would seem that the system doesn't have any way to protect us against that potential for hoarding.

Let me shift to two questions for Dr. Kobayashi. One is, we've talked about the risks of CJD. You were asked earlier about how that would impact your decision to continue to use product. As a physician, how does that affect your prescription for the products? What would you advise patients? In other words, is that a major factor in trying to advise your patients about whether or not they ought to use blood products?

Dr. KOBAYASHI. I believe I would make all the available information that was available to the patient, and then have them give informed consent. I really think it's a patient decision.

Mr. SNOWBARGER. And you wouldn't try to influence that decision whatsoever?

Dr. KOBAYASHI. No.

Mr. SNOWBARGER. Other than the way you give the information.

Dr. KOBAYASHI. No. I think that is an ethical issue that the patient would have to decide for themselves.

Mr. SNOWBARGER. You don't have any particular—let me put it this way: What is your opinion about the risk of CJD?

Dr. KOBAYASHI. I think the risk is extremely remote, but ethically, as a physician, I feel strongly that I cannot require any patient to take any so-labeled product.

Mr. SNOWBARGER. Let's go to label usages, and off-label usages. If you can speak from your experience about—are there concerns within the medical community about the expanded usage of these products for off-label uses, or for expanded label uses, to the point where those who have a critical need may not have access to the product?

Dr. KOBAYASHI. I think your question has two parts. In the area of concerned off-label use, I think that many physicians are concerned, because we don't have adequate studies to evaluate, in some instances, the proper use. On the other hand, I do not think—

the second question is whether we should expand the use. I think that if we have data where IVIG may be beneficial, and there are some indications that there may be, that I personally feel that we ought to do those investigations, and also make IVIG available for those patients that might benefit.

Mr. SNOWBARGER. Well, one of the questions I intend to ask manufacturers when they're before us is, it would appear that they continue to do research on new uses of the same products. My question is, what are they doing to increase their manufacturing capability to meet the new uses of the new products. I mean, I understand the desire to want your product to have a broader market. But if you create a broader market and don't create the production capacity, it seems like we're working against each other at that point.

Thank you, Mr. Chairman.

Mr. SHAYS. I thank the gentleman. It is my intention, given when the House gets out today, to go with our next panel before 1, if all the panelists are here. And we may do that in 5 or 10 minutes. But let me just ask the three of you. Mr. Scheckelhoff, I guess I really need to ask this question, because I could say distributors might choose to inflate the price, but it's also possible that pharmacists could be tempted to do that as well. What is the process for a pharmacist? He knows he's only got, or she's only got, a few patients. You buy a certain allotment. What's the temptation, and how often do you think it happens—to raise the price well above what you paid for it?

Mr. SCHECKELHOFF. And then resell it to the patient at a higher price?

Mr. SHAYS. Yes.

Mr. SCHECKELHOFF. I think that's unlikely. Generally, patients have insurance plans and have many different mechanisms where there are pre-established prices that are reimbursed for product. In a hospital setting, it's very unlikely because many of our patients are on fixed payment plans, per diem rates, capitated rates, and so forth. So I think it's very unlikely in a hospital setting, and I think it's generally unlikely in a retail setting because, again, as the patient's third-party payer reimburses for that prescription, it would be pretty obvious. But I'm not sure that there's any controls to prevent that from happening.

Mr. SHAYS. Now, we haven't really talked about what we think the solutions are. I think this first hearing is just trying to—I mean, we've kind of wanted to know what some may think the solutions are. But the first is just to, I think, understand the depth of the problem as best we can. So this has been very helpful.

Is there anything you would like to, or would have liked us to ask? Then I can ask you the question—you tell me what I should ask you, and you can answer it. Mrs. Hobson, do you have any other closing comment you'd like to make?

Ms. HOBSON. Only that I hope that this issue is resolved quickly, because we do have so many young mothers, so many children. It's a real critical situation, and it involves so many people. So I would hope that this committee and everyone can get together and the issue can be solved.

Mr. SHAYS. I'm going to use this as an opportunity. One of the people in this hearing was a young family. I was curious why two young children and a father and mother were here. The Dunigan family of Winston-Salem, NC came with their 10-year-old son and brother, Gray Dunigan, who has a primary immune deficiency.

Are they here now? I'd like Gray to stand up. Gray, will you stand up? It's nice to have you here, my friend. Now, I understand, Gray, that you have a primary immune deficiency. And I understand that you've missed three doses of IVIG since the shortage began in November, and as a result you have missed 4 weeks of fourth-grade school. Do you work at home when you're not at school?

Mr. DUNIGAN. Yes.

Mr. SHAYS. OK. Well, it's really nice to have you and your mom and dad here, and your brother. You have people who want to help you, both at the table here, and the committee here, and we're going to see what we can do to help you. It's nice to have you. Thank you for coming.

Doctor, do you have any closing comments?

Dr. KOBAYASHI. I would just like to say that I'm impressed by the committee, and the sincerity of the committee, and that I hope we can have a resolution to this quickly in the short term, and also the long term.

Mr. SHAYS. Thank you very much. Mr. Scheckelhoff?

Mr. SCHECKELHOFF. Again, I would applaud the efforts of this group and, I guess, some of Dr. Friedman's comments this morning and would really reinforce or endorse some of his ideas about getting the FDA and some of the manufacturers together. I think that will be a key part of the final solution on this.

Mr. SHAYS. Well, I thank all three of you. We are going to be working together with the Government regulators, the administration, and obviously with the companies that produce products that are sorely needed by so many people. And Mrs. Hobson, we don't want you to have to go to sleep at night wondering how you are going to be able to get immune deficiency, and others who have other needs. And it's nice to see your face and to have you speak out for others. And we'll remember this day and see what we can do.

Ms. HOBSON. Thank you for all your help.

Mr. SHAYS. Thank you. Thank you all.

This hearing is adjourned. This hearing is recessed—I'm sorry, I keep saying this. [Laughter.]

I have no ulterior motive to adjourn on this. [Laughter.]

I am fascinated by this hearing. Stay where you are. Is it a recess—well, we have just a 5-minute-or-less recess before we invite the next panel up. So we'll have a 5-minute recess and then we will start. I will say who is coming to our next panel: Jan Bult, executive director, International Plasma Products Industry Association; Jan Turek, senior vice president and general manager, Biological Products, Bayer Corp.; Gail Gaumer Schulze, senior executive vice president and chief market officer, Centeon; John Bacich, Jr., president, Hyland Division, Baxter Healthcare Corp.; and H. Edward Matveld, president and CEO, Alpha Therapeutic Corp. Invite them to come forward. We'll start in about 4 or 5 minutes.

[Recess]

Mr. SHAYS. I call this hearing to order. We will proceed in the order in which I called you, and actually that is the order into which you're seated.

[Witnesses sworn.]

Mr. SHAYS. For the record, our witnesses have responded in the affirmative. We have five who will give testimony. It would be helpful, probably, to have you stick as close to the 5 minutes, but we will provide the same opportunity. We'll roll it over. But it would be appreciated if you do that.

And one of the things I want to say. If we didn't cover something that's not in your statement, and we didn't ask the question, and you feel it's important for the public record, I'll give you that opportunity in an open question to respond to things you've heard and so on. The purpose of this hearing is to understand the issue, and if you think something needs to be put on the record, we'd like that.

Now, I understand J-A-N is sometimes Jan and J-A-N is sometimes Jan, and we've got a Jan and a Jan, right? [Laughter.]

Jan Bult, start away.

STATEMENTS OF JAN BULT, EXECUTIVE DIRECTOR, INTERNATIONAL PLASMA PRODUCTS INDUSTRY ASSOCIATION; JAN TUREK, SENIOR VICE PRESIDENT AND GENERAL MANAGER, BIOLOGICAL PRODUCTS, BAYER CORP.; GAIL GAUMER SCHULZE, SENIOR EXECUTIVE VICE PRESIDENT AND CHIEF MARKET OFFICER, CENTEON; JOHN BACICH, JR., PRESIDENT, HYLAND DIVISION, BAXTER HEALTHCARE CORP.; AND H. EDWARD MATVELD, PRESIDENT AND CEO, ALPHA THERAPEUTIC CORP.

Mr. BULT. Thank you very much.

Mr. SHAYS. And I would ask you to put the mic a little closer.

Mr. BULT. Good afternoon, Chairman Shays and members of the subcommittee. Thank you for inviting me to testify on this very important issue on the current shortage of intravenous immune globulin, IVIG. I am Jan Bult, executive director for the International Plasma Products Industry Association, representing the four largest commercial fractionators, Alpha Therapeutic, Baxter Healthcare, Bayer Corp., and Centeon.

I will focus on three issues: IPPIA's ongoing effort to provide IVIG data, short-term and long-term measures to address the shortage, and our initial response to the recommendation of the HHS advisory committee on blood safety and availability.

The current IVIG shortage is due to a number of factors occurring simultaneously. First is increased use. Studies by the Marketing Research Bureau indicate that the market for IVIG is increasing around 9 percent per year. We expect this trend to continue. Second, withdrawals to reduce the theoretical risk of Creutzfeldt-Jakob Disease transmission have reduced IVIG supplies. In 1997, over 1,000 kilograms of IVIG were not available for this reason. Finally, facility enhancements to ensure continued regulatory compliance have caused temporary production decreases.

To understand these complex factors, IPPIA members are gathering data with the help of Georgetown Economic Services. A sum-

mary of this data is shown on the charts at the right hand side of the room. I would like ask your permission after my testimony to explain the numbers.

Mr. SHAYS. We'll have everyone go through their testimony, and then we'll allow you to talk about the numbers.

Mr. BULT. Thank you, Mr. Chairman.

The first chart shows the data for the years 1996, 1997, and 1998, and you heard, I will explain the data in a minute. The second chart shows the factors affecting availability. The green boxes contain the same data, but are presented in a different way. And, again, I will explain that in a minute.

These charts correct misconceptions about the shortage. Inventories are significantly reduced, and have reached a current operational level of less than 3 weeks. We are delivering IVIG to patients as quickly as possible. Our companies operate internationally, but approximately 80 percent of the IVIG production is distributed domestically. IVIG pricing reflects normal increases, and does not suggest unreasonable increases.

IPPIA commits to continuing this data collection, and publishing the results every 3 months. This information will help us understand, predict, and respond to the threat of any future shortages. For the short term, IPPIA companies have developed emergency supplies to assist patients in critical need. Also, by providing a larger portion of sales directly to hospitals and pharmacies, IVIG is delivered to patients faster. Through a cooperative effort by industry and FDA, IVIG lot release times have been shortened from the normal 2 to 3 weeks, to 2 to 7 days, without compromising safety.

For the long term, IPPIA members are investing hundreds of millions of dollars to meet the expanding future need of IVIG. Rapid FDA approval of expansion proposals would help to expedite increased IVIG production.

I will now address the HHS advisory committee's recent recommendations. We have already begun data collection and reaffirm our commitment to collect and distribute data on IVIG production and inventories. We encourage other manufacturers to join this effort. We have voluntarily established emergency supplies of IVIG, and we support prioritized use of these emergency supplies. We work for patients' access to safe plasma products, regardless of their location or nationality.

The 1996 data show that the balance of IVIG imports and exports is neutral. Any mandatory change to this balance could cause problems that cannot be quantified. We are committed to providing adequate supplies of safe and efficacious products.

Thank you for considering these very important issues.

[The prepared statement of Mr. Bult follows:]

Mr. Chairman:

My name is Jan Bult. I am the Executive Director of the International Plasma Products Industry Association (IPPIA), the international trade association representing the commercial producers of plasma-based therapies. IPPIA Members produce approximately 80% of the plasma products for the US market, and include the four largest commercial fractionators: Alpha Therapeutic, Baxter Health Care, Bayer Corporation, and Centeon.

The IPPIA appreciates this opportunity to provide the Subcommittee with our views on the current short supply of Intravenous Immune Globulin (IVIG). The IPPIA is aware that during the past few months many hospitals, pharmacies, and most importantly patients, have experienced a shortage of IVIG. The IPPIA will continue to provide accurate information about the current shortage of IVIG - particularly to the patients who depend on the life-enhancing qualities of these products.

My testimony today will focus on four issues:

1. The IPPIA's commitment to an on-going effort to provide data to quantify available supplies of plasma products and determine the causes of the current shortage;
2. Industry's implementation of short-term measures to relieve the shortage;
3. Industry's long-range initiatives to address the shortage; and
4. The IPPIA's initial response to the April 28, 1998 recommendations of the HHS Advisory Committee on Blood Safety and Availability.

Causes of the Shortage – IPPIA Data Collection

Our information indicates that the current IVIG shortage began in late 1997. To better understand the magnitude and causes of this shortage, the IPPIA members have undertaken an intensive data collection effort with the help of Georgetown Economic Services (GES) that I will discuss today.

We believe that the current shortage is due to a number of factors occurring simultaneously. These include:

- Better diagnosis and treatment of patients leading to a continually increasing use of these therapies by physicians seeking to enhance and lengthen the quality of life of their patients;
- Product withdrawals due to the Industry's and the Food and Drug Administration's (FDA) conservative and prudent approach to reducing the theoretical risk of Creutzfeldt-Jakob Disease (CJD) transmission; and

- Temporary production decreases resulting from the implementation of facility/system enhancements and efforts to ensure continued compliance with current good manufacturing practices.

More information on these factors is provided below.

Increasing Demand: While we are not able to quantify the actual demand for these products, studies by the Marketing Research Bureau indicate that the market for IVIG has increased around 9 percent per year for the last several years. At this time, we have no reason to expect any changes in this outlook for the near future.

Effect of CJD Withdrawals: Manufacturers' withdrawal of IVIG from the market due to a theoretical increased risk of CJD transmission (CJD withdrawals) has reduced supplies of this therapy. The following table, which presents data collected by GES, shows the impact of CJD withdrawals by the IPPIA Member Companies on IVIG supplies. The table does not include CJD withdrawals by non-IPPIA companies.

Impact of CJD Withdrawals on IVIG supply

	IPPIA Members		
	1996	1997	1998 (YTD)
Number of Withdrawals	4	6	0
Volume IVIG returned from market (Kg)	16	16	0
Volume of IVIG not released (Kg)	166	1,050	0
Total withdrawals (Kg):	**182**	**1,066**	**0**

These data include the volume of IVIG actually returned from the market and the volume of in-process and unreleased material destroyed as a result of the CJD withdrawals. Over 1000 Kg of IVIG, representing over 40,000 doses, were not available due to CJD withdrawals in 1997. Until a serological test for CJD becomes available, withdrawals for this cause will most likely continue to affect the IVIG supply.

Effect of Facility System Enhancements: IVIG supplies are also affected by temporary production decreases associated with the implementation of enhanced systems to assure continued compliance with current good manufacturing practices. These efforts can be broadly categorized into three areas: quality control/quality assurance enhancements; a changing regulatory environment; and specific production and technical issues. Some of these factors include:

- More frequent and intense FDA inspections resulting in personnel shifts to respond to FDA questions, subsequently leading to longer-than-normal production slow-downs to address compliance issues;
- Changes in the manufacturing process often result in a lower yield of finished product, examples of this phenomena include:
  - Incorporation of additional viral inactivation procedures;
  - Adoption of a donor exposure limitation, commonly referred to as pool size reduction, and;
  - Change of plasma supply source; and
- Other company-specific technical issues.

Each of these factors has resulted in significantly increased production time, with a net result of less IVIG production in 1997 and projected for 1998.

As stated earlier, IPPIA members have undertaken an intensive data gathering effort with the help of Georgetown Economic Services to begin to understand how all these factors affect this complex situation. A summary of these findings is in the following table:

IVIG Supply

	IPPIA Members		
	1996	*1997*	*1998**
IVIG possible supply (Kg)	14,217	14,304	13,956
Withdrawals / recalls /other losses (Kg)	465	1,310	905†
Available supply (Kg)	13,752	12,994	13,051
Domestic Supply (Kg)	11,400	10,331	10,483
Exported Kg)	2,352	2,663	2,568
Inventory on 1/1 (Kg)	1886	1285	788‡
Emergency Supply (Kg)	0	105	430
Average Sales Price (ASP) (Per Gram)	$ 26.57	$ 27.91	

Projected
†Actual Year to Date
‡There was an additional 335-Kg on hold in work in progress inventory for three months pending a CJD investigation. This was released in January of 1998.

These data allow us to correct certain misconceptions regarding the causes of the current IVIG shortage. The chart shows that the IPPIA Member Companies' inventories have reached a very low operational level, from an approximate 6-week supply in 1996 to currently less than 3 weeks. This demonstrates that our companies are making every effort to deliver the therapies as quickly as possible to patients. At the same time, in response to an FDA request, our members have begun to build up an emergency supply (430 Kg in 1998) which is used to serve the most critical patients.

IPPIA Companies operate internationally serving patients in many countries throughout the world. Nevertheless, our data shows that approximately 80% of the IVIG produced in the US by the IPPIA Member Companies is distributed domestically. IVIG pricing by the IPPIA Member Companies reflects normal increases for 1996 to 1997, and is consistent with comparable products. Any suggestion of unreasonable pricing practices by IPPIA Member Companies is absolutely incorrect.

Industry is committed to the health of the patients who depend on these therapies and is taking every appropriate step to help end the current shortage. The IPPIA member companies work day and night to produce adequate supplies of plasma products. However, it is important to note that the current shortage is the result of many factors and there is no single solution. At this time, we cannot estimate how long the current shortage will last.

IPPIA Data Collection Commitment: The IPPIA understands the critical need for IVIG and the seriousness of the current shortage. In this light, we commit to continue our data collection effort. We will collect and make public production data every three months, so that all interested parties will be able to understand the current production trends. We anticipate that this information will allow us to better understand, predict and respond to the threat of any future short supply situations. Additionally, our members have identified both short term and long term initiatives to reduce the impact of the current shortage and reduce the threat of future shortages.

Short-term Initiatives

IPPIA members have implemented emergency programs to assist patients in need. Each IPPIA Member Company is working with the FDA, hospitals, physicians, and patient groups to try to ensure that those patients in critical need have access to these life-enhancing therapies. For this reason, IPPIA members, in response to an FDA request, developed an emergency supply that is reserved for patients in critical need of this therapy. Special telephone numbers provide access for providers and patients to these emergency reserves. In 1998, 430 Kg are committed for this purpose.

Once released through each company's normal quality control procedures, our members are using innovative strategies to quickly deliver this the therapy to the patient. These efforts include providing a larger portion of sales directly to hospitals and pharmacies.

IPPIA members are actively working with the FDA in an effort to get additional IVIG to the market. Through this cooperative effort, FDA's release time for IVIG lots has been shortened from the normal 2-3 weeks to 2-7 days, without compromising safety.

Long-term initiatives

The Industry is also pursuing long-term advancements to address the expanding future medical need for plasma-based therapies, including IVIG. IPPIA members are investing hundreds of millions of dollars in an effort to expand overall capacity at their manufacturing facilities to meet this increased demand. Part of this effort is the development of new yield increasing technologies. Each of our member companies will address their specific actions undertaken to relieve this current situation in their statements to the Subcommittee.

Industry is also increasing human and financial investments to ensure continued compliance. Expedited FDA review and approval of license applications and supplements would be helpful to assure that Industry investments in capacity expansion rapidly result in increased supplies of IVIG and other plasma therapies.

Finally, Industry is developing new technologies that will result in new plasma therapies for the patients who need treatment. Reasonable clinical trial expectations will be instrumental in achieving this outcome.

IPPIA Initial Response to Advisory Committee Recommendations

During its April 27-28, 1998 meeting, the HHS Advisory Committee on Blood Safety and Availability developed short-term and long-term recommendations for addressing the current shortage of immune globulins and certain other plasma products. The Department released a draft of these recommendations on May 1, 1998. While Industry is already addressing many of these issues, we welcome the input of the Advisory Committee and all other interested parties. Our initial response to some of the recommendations follows:

Data collection: The IPPIA reaffirms its commitment to collect and distribute data on IVIG production and inventories. We encourage non-IPPIA manufacturers to join in this effort.

Allocation of Emergency Supplies: In consultation with the FDA, the IPPIA member companies have voluntarily established emergency supplies of IVIG. The IPPIA welcomes any initiative to further develop protocols for prioritizing the use of this emergency IVIG supply.

Imports and Exports: The IPPIA Member Companies are working to assure access to safe and adequate supplies of plasma products for all people who need these therapies regardless of their location or nationality. In this particular case, some Member companies have historical commitments to provide patients with these therapies wherever they are. This may mean exporting these therapies. At the same time, based on 1996 data from the Marketing Research Bureau, other companies import these therapies into the US, and as a result, the balance of trade is neutral. Any mandatory change in this balance may cause other problems that cannot be completely quantified at this time.

Improved FDA Regulations: The IPPIA will explore with the FDA and other appropriate government agencies regulatory reforms that would enhance product safety and availability. Short-term examples could include changing current labeling, disclosure, and resource allocation requirements. For the long-term, FDA could improve product availability by quickly approving Industry license applications and supplements for expanding manufacturing capacity.

Conclusion

In his message to the Advisory Committee, US Surgeon General Dr. David Satcher stressed three themes with respect to blood and plasma products: safety, availability, and trust. The IPPIA agrees that this is a very useful framework for understanding the complex issues that arise in this area. The IPPIA companies are steadfastly committed to providing adequate supplies of safe and efficacious plasma products.

In response to the current supply situation, the IPPIA companies are building trust with their patient communities by forthrightly disclosing production and inventory data and immediately taking steps to assure that emergency supplies reach patients with critical needs. For the long-term, the IPPIA is committed to an ongoing process of data collection and dissemination. The IPPIA Member Companies are also investing more resources in an effort to increase production of IVIG and other plasma therapies to meet increasing medical demand.

The members of IPPIA are working continuously to provide patients with a safe and adequate supply of IVIG and other life-enhancing plasma therapies. Thank you for allowing me to address these very important issues. I would be happy to answer any questions from the Subcommittee.

Mr. SHAYS. Thank you.

Mr. Turek.

Mr. TUREK. Good afternoon, Mr. Chairman, members of the committee.

Mr. SHAYS. Good afternoon.

Mr. TUREK. I'm Jan Turek, head of the biological business worldwide for Bayer Corp. As we informed the HHS committee last week, we really believe it's a privilege and an obligation to help resolve the matter before us, and so I thank you for the opportunity to publicly reaffirm Bayer's commitment to provide its patients with plasma products and recombinant therapies, and to outline the steps Bayer's taking to ensure a safe and increased supply.

Now, because of the unique nature of these products, we establish lifelong relationships with the very special patients that we serve. For that reason, Bayer, like you, is deeply troubled by the current temporary shortage of IVIG. There has been concern expressed that the shortage was artificially created. I'm here to clear that this is not the case. Bayer, with others here today, is determined to end the shortage as quickly as humanly possible.

Now, an unfortunate combination of events have led to this crisis.

First, as we've already heard, the demand for IVIG, including ours, has increased greatly in the last few years as the clinical usefulness of the drug has been recognized in more diseases.

Second, product for many manufacturers was withdrawn or not released to the market because of potential exposure to CJD.

Third, production disruptions occurred at Bayer and other manufacturers. Now, Bayer's disruptions stemmed in part from issues raised during recent FDA plant inspections and from an unexpected breakdown of a key piece of equipment, since repaired, at our sole IVIG manufacturing facility in Clayton, NC.

Fourth, Bayer recognized the shortage and took steps late last year to maintain as great a supply as possible to patients. We depleted our inventories that were scheduled for use in 1998, and provided product to patients in the latter part of 1997.

So, as a result of these factors, we will only be providing about 50 to 60 percent of the amount of IVIG that we supplied in 1997. As for exports, Bayer has for decades been serving patients around the world. As the shortage evolved, we have generally reduced inventories and cut shipments to countries not strongly dependent on Bayer supplies. Now, even in Canada, where Bayer has been the sole contracted supplier for over 10 years, we've worked with the agencies to assure supply goes to patients most in need.

Now, in the short term, here in the United States, to help get product to the neediest patients, Bayer has reserved gammimmunan for patients with pediatric AIDS, or primary immune deficiencies, as well as for general emergencies. In cooperation with the FDA, Bayer and other manufacturers have created special emergency stocks to meet urgent patient needs. Now, I'm also happy to announce publicly today that Bayer has now almost doubled our commitment for these emergency reserves, to ensure that this product available will go to the most needy patients. However, demand still exceeds supply.

Right now, we are working 24 hours a day, 7 days a week in our facility in Clayton and are making significant investment in people and money to return to normal levels of production by the end of this year. Bayer's long-term solutions to develop new products and increase availability is a 20-year-long work in progress, an investment of more than $1 billion. This effort has already resulted in Bayer's Kogenate recombinant Factor 8 to treat hemophilia.

Our commitment to boost IVIG production began back in 1994. As a result, we have a building under construction in Clayton, and we are upgrading a plant in Italy that we purchased in 1996. These measures will boost Gammimmune production by 50 percent over the next few years.

We are also conducting major research into CJD, to find out whether it could be transmitted in blood or plasma and if it could be, how to remove any risks to patients. So we have really demonstrated a willingness to help.

One final point. A recent example of our willingness to help is in response to the Hepatitis A outbreak. The CDC called us to help. We provided 6,000-unit commitment to produce IMIG, even though we have not produced this product for several years. And we're ready to help again.

So, in conclusion, we at Bayer recognize the responsibility we have for thousands of patients who depend on these drugs. They have every right to expect high-quality, dependable products, and we are committed to work with all parties to solve the current temporary shortage and create long-term solutions to ensure an increased supply of these products to our patients.

Thank you very much.

[The prepared statement of Mr. Turek follows:]

Statement of Jan Turek
Bayer Corporation to the
Subcommittee on Human Resources
May 7, 1998

Good afternoon, Mr. Chairman and members of the Committee. My name is Jan Turek, and I am head of Bayer Corporation's worldwide Biological Products business. As we informed the Department of Health and Human Services Advisory Committee last week, we believe it is both a privilege and an obligation to assist in the resolution of the matter before us. And so I thank you for the opportunity to publicly re-affirm Bayer's commitment to provide its patients with plasma products and recombinant therapies and to outline the steps Bayer is taking to ensure a safe and increased supply.

The intrinsic purpose of the Bayer Pharmaceutical organization is to significantly improve health worldwide. Because of the unique nature of these products, we have established a life-long relationship with the very special patients we serve.

We are proud that tens of thousands of patients have benefited from Bayer's immune globulin, Gamimune, since its introduction almost two decades ago. Children and adults who suffer from immune deficiencies can lead healthy, normal lives by using these life-saving products.

For that reason, Bayer, like you, is deeply troubled by the current, temporary shortage of intravenous immune globulin, IVIG. We know that there has been concern expressed that the shortage was artificially-created. I am here to clearly state this is not the case. Bayer, along with others, is determined to end the shortage as quickly as humanly possible.

An unfortunate combination of events have led to this crisis:

First, the demand for IVIG, including Bayer's, has increased greatly in the last few years as the clinical usefulness has been recognized in more and more diseases.

Second, as you have already heard, the worldwide supply of plasma-derived therapies has diminished through products either withdrawn or not released to the market because of potential exposure to CJD -- Creutzfeldt-Jakob Disease.

Third, production disruptions occurred at Bayer and other manufacturers. Bayer's disruptions stemmed in part from issues raised during recent FDA plant inspections and in part from the unexpected breakdown of a key piece of equipment, since repaired, at our sole manufacturing facility, Clayton, North Carolina. We currently are working closely with the FDA to address all regulatory and manufacturing issues.

Fourth, Bayer recognized the shortage early on and took steps in 1997 to maintain as great a supply as possible to patients. We depleted inventory scheduled for use in 1998, and provided this product to patients in the last quarter of 1997.

As a result of these factors, we will produce only about half the amount of IVIG which we had supplied last year.

As for exports, Bayer for decades has been serving patients around the world. As the shortage evolved, we have generally reduced inventories and cut shipments to countries not strongly dependent on Bayer supplies. This would include Spain and Germany, our largest European markets.

Even in Canada, where we have been the sole contracted supplier for 10 years, we worked with agencies to assure supply goes to patients most in need.

Here in the U.S., to help address the distribution of product to the neediest of patients, Bayer is reserving Gamimune-N for children who participated in our pediatric AIDS trials as well as product for distribution by the Immune Deficiency Foundation. Also, in cooperation with the FDA, Bayer and other manufacturers have created special emergency stocks to meet urgent patient needs. However, despite our best efforts, Bayer is unable to provide sufficient product to meet these needs.

Right now, we are making significant investment of people and money to return to normal levels of production by the end of this year.

Bayer's long-term solution to develop new products and increase availability is a twenty-year work-in-progress at an investment of more than one billion dollars.

Ten years of intensive research and development led to Kogenate® recombinant Factor VIII, to treat hemophilia A, which Bayer brought to market in 1993.

Bayer's commitment to boost IVIG production began in 1994. As a result, we have a building under construction in Clayton. We are upgrading a plant in Italy purchased in 1996. These measures will boost Gamimune production by 50% over the next five years.

We also are conducting major research into CJD to find out whether it could be transmitted in blood or plasma – and, if it could be transmitted, how to remove any risk it might pose to patients.

Bayer participates in responsible clinical research to demonstrate appropriate use in new indications. These indications include multiple sclerosis, Kawasaki disease, bone marrow transplant and pediatric AIDS. These studies have all been conducted for the purposes of regulatory approval. Furthermore, since 1978, Bayer has conducted or funded almost one hundred clinical trials on Gamimune products, fifteen of which have been for treatment of infants or children.

Statement of Jan Turek
Bayer Corporation to the
Subcommittee on Human Resources
May 7, 1998

Mr. Chairman, Bayer has demonstrated its willingness to help meet patient needs. A recent example: In response to a Hepatitis A outbreak, the CDC called us to help. We provided a 6,000 unit commitment of IMIG even though we have not produced the product in several years. We are ready to help again.

We at Bayer recognize the responsibility we have to the thousands of patients who depend on these drugs. They have every right to expect high-quality, dependable products. We are committed to work with all parties to solve the current temporary shortage and create long-term solutions to ensure an increased supply of these products to patients.

Thank you.

Mr. SHAYS. Thank you very much, Mr. Turek.

Ms. Schulze.

Ms. SCHULZE. Mr. Chairman and members of the subcommittee, my name is Gail Gaumer Schulze, and I am deputy CEO and senior executive vice president at Centeon. It's my pleasure to be here today to discuss our perspective on this shortage. The shortage is an important issue that we take very seriously, and appreciate the subcommittee's interest in the matter.

As you've heard, and as you know, the current shortage clearly has any number of factors. Some of these have been far more significant to Centeon than other factors. Clearly, we've seen the same increase in demand experienced by others; however, the overriding reason that our 1997 production and distribution of IVIG was lower than it had been in prior years was due to temporary suspension of production, and other reductions in output that were involved in the implementation of an enhanced quality system.

Other than 1997, we have maintained IVIG capacity at the plant's maximum level. Centeon's enhanced quality system is a result of our ongoing commitment to the production of high-quality products. As such, the Q–A checks implemented within our manufacturing standard operating procedures approximately doubled the time it takes to produce, review, and internally approve product for distribution. These measures, and other plant activities, contributed to a 1997 run-rate of IVIG that was 70 percent less than it was in prior years. Please note that this was true for all the other products we made in our U.S. facility as well.

As you may know, Centeon entered into a consent degree with the Federal Government in January 1997. Thereafter, we continued to implement many significant new processes and procedures within our facility. Here are some examples: we nearly doubled our quality assurance-quality control staff; increased facility operation staff 25 percent; increased the amount of training with over 45,000 labor hours in 1997, and 25,000 already this year; implementing significant capital investments; incorporating a tenfold increase in the number of validation professionals; and revising several thousand manufacturing documents and control documents since the beginning of 1997.

I am confident that as this enhanced system becomes increasingly incorporated into our production and quality processes, our IVIG output will grow. In fact, the level of production for IVIG for this year is scheduled to approach our 1995 amount, which was our highest level ever. This is essentially the current maximum capacity of the facility for immune globulin.

Clearly, this is an encouraging development and our 1998 output should help the supply problem. Nevertheless, we will continue to maintain the measures we implemented to assist in emergency needs during this time period. We will maintain our program to supply IVIG to critical care requests we receive from doctors. We will continue to work closely with patient groups. And we will continue to work with our hospitals and our group purchasing partners who have emergency needs.

Finally, Centeon will continue to work closely with FDA to obtain lot releases in expeditious fashion, and we greatly appreciate FDA's assistance in this effort. On a longer-term basis, we are continuing

to explore options for expanding capacity. We are very aware the growth rate in demand approaches 10 percent a year. We continue to evaluate production, product, and specification enhancements that will help address that growth, and we are internally challenging our time lines and our thinking in the hopes of moving faster.

However, I don't want to leave the impression that I'm over promising. Our first and foremost commitment is to ensure the enhanced quality systems that we have implemented remain robust, and that future production changes remain consistent with this commitment to compliance. Any growth in capacity that may be implemented will be fully consistent with this commitment.

The chairman's invitation also highlighted two other points: pricing and exports. The average selling price of IVIG to our customers remained essentially unchanged from 1996 to 1997. I will quickly add, however, that we believe future prices will need to reflect the substantially increased capital expenditures, plasma costs, and personnel costs associated with the implementations I just described. The cost of production has climbed significantly, and it is unlikely to return to prior levels. It is also important to note that we do not expect to ever recapture fully these increased business expenses.

Regarding exports, although we are a global company, the vast bulk of our U.S. production is targeted for North America. We exported a very small percentage of IVIG over the past 2 years, and during the current year, we expect it to be similarly limited.

The final issue I'd like to address is our intramuscular immune globulin. As the subcommittee may know, we received regulatory approval from the FDA for the pasteurized IGIM earlier this year, and expect to begin production momentarily.

In conclusion, Mr. Chairman and members of the subcommittee, Centeon is 100 percent committed to producing and distributing IVIG and IGIM as fast as we humanly can, and at our maximum capacity. We have never stockpiled, we have never price-gouged, and to the best of our knowledge, we never entered into relationships with any other party that has. We clearly focus our output on the needs of patients of the United States, and we believe our commitment to quality in the long run is the ultimate benefit of the patients.

We look forward to continuing to work with all of the concerned parties, including this subcommittee, on this and other important issues. Thank you.

[The prepared statement of Ms. Schulze follows:]

MR. CHAIRMAN AND MEMBERS OF THE SUBCOMMITTEE, MY NAME IS GAIL GAUMER SCHULZE AND I AM DEPUTY CEO AND SENIOR EXECUTIVE VICE PRESIDENT OF CENTEON. IT IS MY PLEASURE TO BE HERE TODAY TO DISCUSS CENTEON'S PERSPECTIVE ON THE CURRENT IMMUNE GLOBULIN SHORTAGE.

THIS SHORTAGE IS AN IMPORTANT ISSUE THAT WE AT CENTEON TAKE VERY SERIOUSLY, AND WE APPRECIATE THE SUBCOMMITTEE'S INTEREST IN THE MATTER. BASED UPON THE CHAIRMAN'S INVITATION, I WILL FOCUS MY PRESENTATION ON TRYING TO HELP THE SUBCOMMITTEE DETERMINE THE CAUSES OF THE CURRENT AND CHRONIC SHORTAGES OF IMMUNE GLOBULIN PRODUCTS, AS WELL AS DEVELOP SHORT AND LONG-TERM SOLUTIONS.

AS YOU WILL HEAR FROM VARIOUS SPEAKERS, THE CURRENT SHORTAGE HAS CLEARLY BEEN CAUSED BY SEVERAL CONCURRENT FACTORS. ADDED TOGETHER, THESE FACTORS HAVE CONTRIBUTED TO A PRODUCT SHORTFALL THAT HAS BEEN A CONCERN FOR PATIENTS, PHYSICIANS AND THE IMMUNE GLOBULIN INDUSTRY.

SOME OF THE FACTORS CONTRIBUTING TO THE SHORTAGE HAVE BEEN MORE SIGNIFICANT TO CENTEON THAN SOME OF THE OTHER REASONS

MENTIONED. CLEARLY WE HAVE SEEN THE SAME INCREASE IN DEMAND EXPERIENCED BY OTHERS. HOWEVER, THE OVERRIDING REASON THAT OUR 1997 PRODUCTION AND DISTRIBUTION OF IGIV WAS LOWER THAN IT HAD BEEN IN PREVIOUS YEARS WAS DUE TO TEMPORARY SUSPENSIONS OF PRODUCTION, AND OTHER REDUCTIONS IN OUTPUT, THAT WERE INVOLVED IN THE IMPLEMENTATION OF OUR ENHANCED QUALITY SYSTEM.

CENTEON'S ENHANCED QUALITY SYSTEM IS A RESULT OF OUR ON-GOING COMMITMENT TO THE PRODUCTION OF HIGH QUALITY PRODUCTS. AS SUCH, THE QUALITY ASSURANCE CHECKS IMPLEMENTED WITHIN OUR MANUFACTURING STANDARD OPERATING PROCEDURES SIGNIFICANTLY INCREASED THE TIME IT TAKES TO PRODUCE, REVIEW AND INTERNALLY APPROVE PRODUCT FOR DISTRIBUTION. THESE MEASURES, AND OTHER PLANT ACTIVITIES, CONTRIBUTED TO A 1997 RUN RATE OF IGIV THAT WAS SIGNIFICANTLY LESS THAN WHAT IT HAD BEEN IN PREVIOUS YEARS. PLEASE NOTE THAT THIS WAS TRUE FOR ALL THE OTHER PRODUCTS MADE IN OUR U.S. FACILITY DURING 1997 AS WELL.

CENTEON HAS BEEN IMPLEMENTING THIS SYSTEM AS RAPIDLY AS POSSIBLE, AND I THINK IT WOULD BE HELPFUL IF I BRIEFLY DESCRIBED

SOME OF THE ACTIVITY ASSOCIATED WITH THIS EFFORT. AS THE SUBCOMMITTEE MEMBERS MAY KNOW, CENTEON ENTERED INTO A CONSENT DECREE WITH THE FEDERAL GOVERNMENT IN JANUARY OF 1997. THEREAFTER, WE CONTINUED TO IMPLEMENT MANY SIGNIFICANT PROCESSES AND PROCEDURES WITHIN OUR FACILITY. THESE INCLUDE:

- NEARLY DOUBLING OUR QUALITY ASSURANCE/QUALITY CONTROL STAFF;
- INCREASING OUR FACILITY OPERATIONS STAFF BY 25%;
- INCREASING THE AMOUNT OF TRAINING, WITH OVER 45 THOUSAND LABOR-HOURS BEING CONDUCTED LAST YEAR AND 25 THOUSAND LABOR-HOURS ALREADY COMPLETED THIS YEAR;
- IMPLEMENTING SIGNIFICANT CAPITAL INVESTMENTS AT THE FACILITY;
- INCORPORATING A TEN-FOLD INCREASE IN THE NUMBER OF VALIDATION PROFESSIONALS INVOLVED WITH NEW EQUIPMENT VALIDATIONS AND EXISTING EQUIPMENT REVALIDATIONS; AND
- REVISING SEVERAL THOUSAND MANUFACTURING DOCUMENTS AND CONTROL DOCUMENTS SINCE THE BEGINNING OF 1997.

I AM CONFIDENT THAT AS THIS ENHANCED SYSTEM BECOMES INCREASINGLY INCORPORATED INTO OUR PRODUCTION AND QUALITY CONTROL PROCESSES, OUR IGIV OUTPUT WILL GROW. IN FACT, THE

LEVEL OF PRODUCTION OF IGIV FOR THIS YEAR IS SCHEDULED TO APPROACH OUR 1995 AMOUNT, WHICH WAS OUR HIGHEST LEVEL EVER. THIS IS ESSENTIALLY THE CURRENT MAXIMUM CAPACITY OF THE FACILITY FOR IMMUNE GLOBULINS.

CLEARLY, THIS IS AN ENCOURAGING DEVELOPMENT, AND OUR 1998 OUTPUT SHOULD HELP TO AUGMENT SUPPLY. NEVERTHELESS, WE WILL CONTINUE TO MAINTAIN THE MEASURES WE HAVE IMPLEMENTED TO ASSIST IN ADDRESSING EMERGENCY NEEDS FOR IGIV DURING THIS PERIOD. FOR EXAMPLE, WE WILL MAINTAIN A PROGRAM WITHIN OUR MEDICAL AFFAIRS DEPARTMENT THAT SEEKS TO SUPPLY IGIV TO CRITICAL CARE REQUESTS WE RECEIVE FROM DOCTORS. WE WILL ALSO WORK CLOSELY WITH PATIENT GROUPS WHO MAY FORWARD REQUESTS TO US. AND WE WILL WORK WITH HOSPITALS AND GROUP HOSPITAL PURCHASING ORGANIZATIONS WHO HAVE EMERGENCY NEEDS WITHIN THEIR HOSPITALS. FINALLY, CENTEON WILL CONTINUE TO WORK CLOSELY WITH FDA IN OBTAINING LOT RELEASES IN AN EXPEDITIOUS FASHION, AND WE GREATLY APPRECIATE FDA'S ASSISTANCE IN THIS EFFORT.

ON A LONGER-TERM BASIS, WE ARE CONTINUING TO EXPLORE OPTIONS FOR EXPANDING OUR PRODUCTION CAPACITY TO MEET THE INCREASE

IN DEMAND. WE ARE VERY AWARE THAT THE GROWTH RATE IN DEMAND FOR IGIV APPROACHES 10 PERCENT EACH YEAR. WE WOULD LIKE TO IMPLEMENT STRATEGIES AND PRODUCTION ENHANCEMENTS THAT COULD HELP TO ADDRESS THAT GROWTH, AND WE ARE INTERNALLY CHALLENGING OUR TIMELINES IN THE HOPES OF MOVING FASTER.

HOWEVER, I DO NOT WANT TO LEAVE THE IMPRESSION THAT I AM OVER-PROMISING. OUR FIRST AND FOREMOST COMMITMENT IS TO ENSURE THAT THE ENHANCED QUALITY SYSTEM WE HAVE IMPLEMENTED REMAINS ROBUST, AND THAT FUTURE PRODUCTION CHANGES REMAIN CONSISTENT WITH OUR COMMITMENT TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICES. ANY GROWTH IN CAPACITY THAT MAY BE IMPLEMENTED WILL BE FULLY INCORPORATED INTO THIS COMMITMENT TO QUALITY.

THE CHAIRMAN'S INVITATION ALSO HIGHLIGHTED TWO OTHER POINTS -- PRICING TRENDS AND EXPORTS. THE AVERAGE SELLING PRICE OF IGIV TO OUR CUSTOMERS REMAINED ESSENTIALLY UNCHANGED FROM 1996 TO 1997. I WILL QUICKLY ADD, HOWEVER, THAT WE BELIEVE FUTURE PRICES WILL PARTIALLY REFLECT THE SUBSTANTIALLY INCREASED CAPITAL EXPENDITURES, PLASMA COSTS, AND PERSONNEL COSTS

ASSOCIATED WITH THE IMPLEMENTATION OF THE ENHANCEMENTS I DESCRIBED. THE COST OF PRODUCTION HAS CLIMBED SIGNIFICANTLY, AND IT IS UNLIKELY TO RETURN TO PRIOR LEVELS. IT IS ALSO IMPORTANT TO NOTE THAT WE DO NOT EXPECT TO EVER FULLY RECAPTURE THESE INCREASED BUSINESS EXPENSES.

REGARDING EXPORTS, ALTHOUGH WE ARE A GLOBAL COMPANY, THE VAST BULK OF OUR U.S. PRODUCTION IS TARGETED FOR NORTH AMERICA. WE EXPORTED LESS THAN FOUR PERCENT OF OUR IGIV OVER THE PAST TWO YEARS. DURING THIS CURRENT YEAR, WE ANTICIPATE EXPORTS OUTSIDE OF NORTH AMERICA TO BE AROUND THAT SAME LEVEL.

A FINAL ISSUE THAT I WOULD LIKE TO ADDRESS IS OUR INTRAMUSCULAR IMMUNE GLOBULIN. AS THE SUBCOMMITTEE MAY KNOW, WE RECEIVED REGULATORY APPROVAL FROM THE FDA FOR OUR PASTEURIZED IGIM EARLIER THIS YEAR. THIS APPROVAL CAME AFTER WE WORKED CLOSELY WITH FDA IN FINALIZING AND SUBMITTING OUR PRODUCT LICENSE APPLICATION. WE HAVE RECENTLY CONCLUDED AND SUBMITTED OUR ESTABLISHMENT LICENSE APPLICATION FOR APPROVAL, AND WE EXPECT TO BEGIN PRODUCTION OF OUR IG-PIM IN THE VERY NEAR FUTURE. WE WILL WORK AS RAPIDLY

AS POSSIBLE -- CONSISTENT WITH OUR COMMITMENT TO QUALITY -- TO DISTRIBUTE THAT PRODUCT ONCE LOTS ARE PRODUCED AND RELEASED.

IN CONCLUSION, MR. CHAIRMAN AND MEMBERS OF THE SUBCOMMITTEE, CENTEON IS COMMITTED TO PRODUCING AND DISTRIBUTING IGIV AND IGIM AS QUICKLY AS POSSIBLE, AND AT A CAPACITY LEVEL. ADDITIONALLY, OUR COMMITMENT TO QUALITY WILL HELP TO ENSURE A CONSISTENT SUPPLY OF HIGH QUALITY THERAPIES PRODUCED IN STRICT ACCORDANCE WITH CURRENT GOOD MANUFACTURING PRACTICES.

WE LOOK FORWARD TO CONTINUING TO WORK WITH PATIENT GROUPS, CLINICIANS, THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA, AND THIS SUBCOMMITTEE ON THIS AND OTHER IMPORTANT ISSUES.

THANK YOU.

Mr. SHAYS. Thank you, Miss Schulze.

Mr. Bacich? Is that like Kasich?

Mr. BACICH. No, it's Bacich.

Mr. SHAYS. Bacich.

Mr. BACICH. But it's close.

Mr. SHAYS. OK.

Mr. BACICH. Good afternoon, Mr. Chairman and members of the subcommittee. I'm John Bacich, president of Baxter's Hyland Division. I began at Baxter more than 30 years ago, after earning my degree in microbiology, and since then have worked in almost every facet of the plasma protein field. In my present capacity, I've directed the design, construction, and expansion of biotech facilities worldwide. This also includes the expansion of Gammagard S/D production, which has gone from approximately 150,000 equivalent vials to about 3 million vials over a 12-year period.

I recently announced my retirement, but I take great pride in being part of a company that is responsible for saving and improving lives, and I welcome this chance to apprise both you and the public of our deep concern about this health issue, that is, the shortage of intravenous immunoglobulin, IVIG. As a major supplier of such therapeutics, marketed under the trade name Gammagard S/D and Polygam S/D, which we make for the American Red Cross but do not market or sell, I want to make two things clear at the outset.

First, we at Baxter are committed to providing adequate supplies of safe and effective plasma protein therapeutics now and in the future, and we work closely with the FDA and other regulatory bodies, physicians, and, most important, patients to achieve this goal.

Second, the people at Baxter are making every effort to optimize our production capacity in both the United States and abroad in order to supply our products to every patient who needs it. It is important that you know that Baxter's production facilities have been operating 24 hours a day, 7 days a week for years to meet the growing demand of our products. As the shortage became apparent, we responded by taking four specific actions.

First, it has been standard practice to hold a small inventory in reserve for patients with acute needs, and we have increased our reserves to a 14-day supply. Second, we began allocating our products to our customers in a further effort to make sure that patients who needed them could obtain them. Third, we also deferred new clinical research that would require use of any Gammagard S/D. Fourth, we asked the FDA for permission to release product more quickly after production so it gets to our patients sooner.

As helpful as those actions were, we at Baxter have been receiving more than 50 calls a week from patients whose stories are similar to the ones you heard this morning. So we have taken some additional steps to alleviate the overall shortage.

First, we have applied to the FDA to allow us to import a product called Endobulin from our facility in Vienna, which would add up to 150,000 vials a year from a European source. Second, we have begun processing an additional 150,000 vials at our IVIG processing plant at Rochester, MI, anticipating that the FDA will approve a license amendment that allows increased production there. So those combined contributions would be about 300,000

vials. And third, as an outgrowth of our consistent expenditures for research on blood therapies, we are employing new technology to increase the output at our various processing facilities.

So those are some of the steps we have taken to remedy what all of us recognize is a very serious situation. But at this point I would like to address an equally serious and unfounded allegations that have appeared in various reports on this problem, and they concern stockpiling, exports, and unfair pricing.

First of all, I can state unequivocally that Baxter has never ever stockpiled any of our plasma protein therapeutics. It's very difficult to even maintain the 14-day emergency supply that I mentioned earlier. As to exports, let me say that we're well within the aggregate that you've heard from Mr. Bult, and moreover we import a plasma-based product from Europe for patients with special needs here. And, as I mentioned, we hope to import more upon receiving FDA approval.

Finally, on any allegations of price increases by companies hoping to capitalize on the shortage, I can tell you that our prices today in 1998 are actually less than they were in 1994, when we launched this product.

So in conclusion, Mr. Chairman, I ask that no one on the committee fail to realize that we at Baxter are fully aware that patients' lives depend on our efforts. We're committed to providing safe and effective therapies, and believe our response to the current situation has been quick, decisive, and responsible. We're producing more now, importing more now, and look forward to doing even more in the months ahead.

We appreciate this opportunity to tell you of our efforts, because we think a frank and open dialog can most effectively help us respond to the scientific and health care challenges that confront us each day. Thank you for your attention.

[The prepared statement of Mr. Bacich follows:]

INTRODUCTION

Good morning, Mr. Chairman and members of the Committee. I am John Bacich, the president of the Hyland Division of Baxter Healthcare Corporation.

I joined this company 30 years ago, as I worked my way through college and earned a bachelor's degree in microbiology. I have served in a variety of capacities and worked in every facet of the plasma protein field, including biologics procurement, production, quality assurance, plant management, and eventually managing Baxter's plasma protein business. As president, I have directed the design, construction and expansion of plasma fractionation and biopharmaceutical facilities worldwide. Recently, I announced my intention to retire this July. I can look back over my thirty-year career as a period in which this industry has undergone profound changes, weathered significant challenges and now stands poised on the brink of tremendous technological breakthroughs. I am proud to be part of a company that is responsible for saving and improving lives, everyday, wherever patients are in need.

In coming here today, I welcome the opportunity to apprise you and the public of our deep concern about an important health issue that your Committee has under consideration. In brief, the issue centers on a serious shortage of a vitally needed medical substance known as intravenous immunoglobulin, a protein therapeutic derived from human blood plasma.

As a major supplier of intravenous immunoglobulin, or IVIG, under the trade names Gammagard® S/D and Polygam® S/D (the latter prepared by us for the American Red Cross), we at Baxter are confident that we have the expertise to address these concerns.

BAXTER'S ACTION PLAN

Today I want to provide assurances on the following points:

- Baxter is committed to providing adequate supplies of safe and effective plasma protein therapeutics now and in the future, and works closely with the U.S. Food and Drug Administration (FDA) and other regulatory bodies, physicians, and patients to achieve that goal.

- The people of Baxter are working diligently to optimize our production capacity both in the United States and overseas to process and reliably supply IVIG for patients who need these vital therapies.

It is important for the Committee to know that we at Baxter have been operating 24 hours a day, seven days a week to meet the growing demand for IVIG. Last year we recognized that there might be a shortage of IVIG when one company stopped production. Baxter began monitoring orders and deliveries and placed customers on allocation in order to balance needs and available supply for patients throughout the United States.

Once the supply shortage became apparent in November 1997, Baxter implemented an action plan incorporating immediate, short-term and longer-range solutions to alleviate the insufficient supply of IVIG therapies. We immediately:

- Expanded our emergency reserve to 14 days to ensure that patients with critical needs were supplied;
- Deferred new clinical research using IVIG which would reduce available supplies;

- Obtained FDA permission to release some IVIG more quickly after production; and,

- Continued to work with the FDA, physicians, patient groups and others to ensure that critical needs were met during the shortage.

In the short-term, we:

- Modified schedules at two facilities to increase production of an intermediate form of IVIG for processing at other plants -- which could add 150,000 vials of IVIG in the United States this year, once FDA approval is received; and

- Requested authority from the FDA to import an IVIG product from our facility in Austria which could provide an additional 75,000-150,000 vials in the United States, once FDA clearance is received.

Over the long-range, Baxter will continue to make extensive investments in facilities and new processing technologies both at home and abroad to provide steady improvement in the quality, quantity and safety of plasma protein therapies. We invest more than $1 million each day in research and development, more than one half of which is allocated to our businesses involved with plasma fractionation, recombinant therapies, blood collection and separation devices, and hemoglobulin therapeutics.

CAUSES OF THE SHORTAGE

For many years, there have been shortages throughout the world of plasma-based therapies, including IVIG. The current shortage is due to a number of factors occurring simultaneously, including:

- Better diagnosis and treatment of patients;

- Continually increasing use of these therapies by physicians seeking to enhance and lengthen the quality of life of their patients;

- Product withdrawals due to the industry's and the FDA's conservative and prudent approach to reducing the theoretical risk of these products transmitting various diseases; and,

- Temporary production decreases to ensure good manufacturing practices. Two of the industry's major plasma fractionators had to interrupt production for a number of months while they revised manufacturing procedures in order to resolve regulatory issues.

IVIG THERAPEUTICS -- PREPARATION AND USE

I'd like to give the Committee some insights into exactly what is at the heart of the matter. Specifically, what is the substance known as IVIG, how is it produced and used, and what are some factors behind the current shortage?

In plain language, immunoglobulins are proteins produced by one or more of a particular type of cell within the body's immune system. Also known as antibodies, they play the major role in combating disease. Intravenous immunoglobulin is a concentrated solution of immunoglobulin prepared from a pool of human plasma and given intravenously, as compared with a similar product that may be given intramuscularly (into muscle tissue) and is known as IMIG.

Since first made available in 1986, Baxter's IVIG therapeutics have been used with FDA approval to replace dysfunctional immunoglobulin in patients who have a primary immune deficiency. IVIG is also used to bolster the health of persons with acquired abnormalities of the immune system, such as pediatric AIDS and chronic lymphocytic leukemia.
Our Gammagard® S/D has also proven to be effective in treating immune thrombocytopenic pupura (ITP). The FDA has approved its use for all these purposes.

As more and more physicians have become familiar with the benefits of IVIG, they have concluded that these therapeutics are safe, reliable and useful for the treatment of an increasing

number of diseases. Consequently, our products and those of others have become subject to what is known as "off-label" (non-FDA-approved) usage. That is, they are increasingly being prescribed for patients with a variety of serious conditions which physicians believe may respond positively to treatment. In some situations, the positive results of this therapy have been reported in medical and scientific journals. An example is in treatment of Guillain-Barré syndrome, a devastating acquired neurological condition that results in paralysis. The success of Gammagard® in the management of this disease was reported in The New England Journal of Medicine and subsequently this indication has been approved in many European countries, but not in the United States.

LEGACY OF INCREASING IVIG DEMAND

The important benefits of this therapeutic biologic for many patients with serious immune-caused diseases and better diagnosis by physicians have caused IVIG use to increase progressively since its introduction. Even though some alternate therapies have at least partially displaced IVIG in the treatment of some diseases, and even though production has grown steadily, demand for this therapeutic today exceeds supply.

It is important to note that in efforts to meet the present demand for IVIG, Baxter is operating its domestic production facilities 24 hours a day, seven days a week. Our production levels in 1996, 1997, and thus far in 1998 are very similar. Yet we are able to fill only about 90 percent of the current contractual commitments for our IVIG therapeutics, leaving us with no choice but to allocate supplies to our customers.

In addition, we at Baxter have been receiving many letters and calls from individuals who are in desperate need of plasma-derived therapies made by other processors. These patients have been told by their physicians or health-care providers that the product they rely on is unobtainable, or out of stock, or delivery is expected sometime in the future. Currently, Baxter is concentrating on meeting the essential needs of all users of our Gammagard® S/D, and we regretfully must

say that we are unable–except in life-threatening emergency situations – to accommodate requests from patients whose other medicines are unavailable.

PREPARING IVIG — FROM PLASMA DONOR TO PATIENT

Having briefly discussed the growing demand for IVIG products, I'd like to turn to the "supply" side of the equation. This will involve detailing some of the complexities that must be taken into account when attention is focused on *increased production* as the solution to a shortage of this nature.

Because our therapeutics are made from the blood plasma of human donors and are intended for use within the bloodstream of other humans, the products must be more than merely reliable and effective. They must be as safe as they can possibly be.

Our focus is solely on patient welfare. Everyone at Baxter, along with the FDA, this Committee, outside critics, and our competitors help keep our focus on that single objective: patient welfare.

With that in mind, I'd like to take you briefly through the basic steps required to process Gammagard® S/D.

Plasma Collection

Plasma collection begins with the people who willingly provide the raw material – human plasma, known as source plasma. Plasma donors, who receive compensation for roughly 90 minutes of their time, undergo a process called plasmapheresis at collection centers. During that time, a machine automatically and in a continuous cycle separates the cellular blood components from the plasma and returns them to the donor. This process enables us to obtain more than three times the amount of plasma from a single donation than can be obtained from a unit of whole blood. In addition, while whole-blood donors are permitted to give blood

approximately once every eight weeks (and the average is considerably less), plasma donors can volunteer as often as twice a week if they so desire - and many, in fact, do so.

With safety uppermost in mind and the dangers of potentially infectious units well recognized, a detailed procedure has been developed and implemented that greatly limits the number of people who are eligible to serve as donors. A thorough questionnaire is used to screen out any applicant who appears to have specific risk factors or who has had cancer, hepatitis, leukemia, malaria, HIV, or a host of other illnesses or conditions, including a potential for Creutzfeld-Jakob Disease (CJD). Furthermore, the donor's name and identification are checked against a list of donors who have been previously deferred either for a period of time or permanently. New donors also undergo a physical examination, which is repeated annually.

These safety precautions only begin with screening. A sample of each and every donated plasma unit is tested for viral and other infections. Our industry and the FDA have acted with great speed and purpose to implement ever-tighter regulations and procedures on testing, and the donated plasma is held back from processing for at least 60 days until sufficient checks have been done and donation records are verified. If any unit tests positive and subsequent testing confirms the problem, the plasma unit is immediately destroyed, as well as any other units given by the same donor. And, the donor's name goes on a list of permanently excluded donors that is nationally distributed to all collection centers.

Separation and Preparation

Similarly, there are restrictions and safeguards at each step of the process that produces IVIG from collected plasma. Known as fractionation, the process separates the specific protein molecules and other elements within the plasma from each other. For each therapeutic (IVIG, clotting factor, etc.), enough of the specific protein must be collected, combined and treated to prepare as an injectable substance that will provide a therapeutic effect.

To obtain enough protein of a specific type to make these medicines for patients in need, plasma units from a maximum of 60,000 donors are carefully thawed from their frozen state and blended in sterile vats with a mixture of water and alcohol. From this single pool of plasma, a number of different therapeutics can be produced, as sequential variations in the temperature, pH, and alcohol concentration cause one or another protein molecule to separate from the whole. It is important to note that with each change, a different molecule is drawn off, and its presence or absence can affect the processor's ability to obtain other products at later steps in the process.

Viral Inactivation

As desired proteins separate from the solution, they are harvested via a filtration system, or by spinning the solution at high speed in a centrifuge. At this point, I want to state that the fractionation process itself destroys or inactivates viruses that might be present in the plasma solution. They are rendered harmless by the applications of heat, by the alcohol, and by the variations in the pH levels. But in an additional and important safety measure, Baxter adds solvents and detergents -- the S/D in Gammagard® S/D -- for an even safer product.

In final stages, measures are taken to purify the product by removing the alcohol, solvents and detergents via additional filtration or by a freeze-drying process, leaving only the desired therapeutic protein. For some specific immunoglobulins, yet another purification technique uses a procedure known as ion-exchange chromatography. Much like iron filings can adhere to a magnetic plate, proteins that carry a charged ion can be made to cling to a similarly charged surface as the liquid solution flows over it. The proteins are then captured and treated to make them suitable for intravenous injection.

Now, at every step of this complex production procedure, Baxter must - and does - adhere to stringent Good Manufacturing Practice requirements set by the FDA, the World Health Organization, the Pharmaceutical Inspection Convention, and various other international bodies. These guidelines and requirements not only cover the production process, but affect

organization and personnel, building and facilities, equipment, packaging and labeling, and records and reports.

And I can state that the system works, and works superbly: of the millions of vials of plasma derivatives produced last year by Baxter and the other members of the International Plasma Products Industry Association, not one had to be withdrawn because of a known danger of viral transmission.

CONSTRAINTS ON MODIFYING THE PROCESS

I want to make one point very strongly. *The entire process of producing and delivering a plasma-derived product rests on a series of interconnected steps and procedures.* If any one alteration were made, it would require extensive modifications in all the other variant factors that are part of the production process -- and each of those steps would call for extensive research, validation and FDA approval before it could be implemented.

We at Baxter are concerned that any major changes that are introduced -- or suggested for introduction -- anywhere in the process might have adverse consequences at another point. It has been suggested, for example, that producing our products from *smaller* donor pools would reduce the likelihood of a problematic donor's plasma adversely affecting patients who receive the therapeutics. However, the industry has found that the use of smaller pools makes the fractionation process less efficient and that a proportionally reduced amount of product is obtained.

We are operating the main fractionation facilities that produce Gammagard® S/D at capacity. We are filling the tanks, conducting the fractionation process, and refilling the tanks as rapidly as possible. The fractionation process cannot be speeded up. We cannot simply add new tanks; that would require expansion or construction of a new facility, which would take many years. And, we cannot add any more days to the week or weeks to the year. If we were now forced to reduce pool size further, in effect filling the tanks half-full or less, then our output would be

reduced accordingly. This is because the number of tanks and the time to process the plasma is constant, but now only half the material would be processed.

Equally important, even when the intent is to enhance safety procedures during the production process, a mandated change might reduce the *efficacy* of the needed therapeutic protein, with the result proving truly detrimental to patients. If Baxter were compelled to introduce such a radical change today, this Committee might well find itself conducting a hearing into even greater product supply constraints.

It is also important to be aware that Baxter's present facilities -- like most others in the industry -- were designed and built in accordance with what were viewed as realistic projections of both future demand and the investment needed to meet it. The time needed to construct not only a production facility but the infrastructure that must go with it -- donor collection centers, warehousing, laboratory testing, filling and labeling equipment, and staff -- can cover a span of five years or more. All along the way, data must be collected, analyzed and reviewed both by us and the FDA to ensure that the therapeutics that result from the extensive investment of time, talent and financial resources will be both effective and safe.

And, I reiterate that during this process no major changes in any step are permitted without FDA approval following its review and examination of supporting clinical data. This is time-consuming, but this is the way that it should be. We recognize that fact because we are fully aware that we deal with rare and fragile protein molecules, which under certain circumstances can be harmful to the patient. As much as we often would like to move with greater speed ourselves, or to have the regulatory and investigative bodies that affect our industry proceed more quickly, we must proceed responsibly and cautiously.

There are still other factors that have affected the supply situation. As you know, and as much of the public is aware, the plasma products industry over the years has been required to recall product for various reasons. Concern about the theoretical risk of transmission of CJD has led to even more precautionary recalls. As the members of this Committee were told last summer

by the National Institutes of Health (NIH), the risk of CJD transmission by blood or blood products is theoretical; there has never been scientific documentation of even a single case of CJD transmission by blood or blood products.

Nonetheless, increasingly throughout the industry these lots of withdrawn or recalled product are destroyed or discarded as a precautionary measure to comply with FDA recommendations. The result has contributed -- as was predicted -- to a further temporary shortage of product.

OTHER CONSIDERATIONS

There are yet other factors that affect the amount of IVIG that reaches the patient.

At the present time there are a half-dozen different IVIG products available in the United States from different processors. In fractionating human blood plasma to produce an IVIG intended for treatment of specific conditions or illnesses, each company employs a different process. Each patient is an individual, with his or her own tolerances. Just as some people's systems cannot tolerate a particular "brand name" painkiller when a different "brand name" painkiller medication is prescribed, so an IVIG from an alternate supplier cannot simply be substituted if the patient's customary IVIG is not available. Patients can experience side effects and react differently to different specific IVIG products. Baxter's Gammagard® S/D, for example, is the only licensed therapeutic indicated for patients who can experience serious reactions to an IgA protein foreign to their own bodies.

RESPONSIBLE DELIVERY AND PRICING

Now, once our therapeutics are processed, packaged and labeled with great care, we sell them almost entirely to health-care providers -- to hospitals, physicians, and home care companies with a pharmaceutical license. Very little -- less than 5 percent -- goes to brokers or middlemen.

As a reliable long-time supplier of safe and effective IVIG, Baxter practices responsible pricing. To illustrate, the Bureau of Labor Statistics' Medical Price Index has risen some 15.3 percent over the last four years. But Baxter's price of Gammagard® S/D is less today than at the time of the product's introduction in 1994. Our customers, in turn, set their own prices to patients.

With a fair pricing policy and with demand growing, Baxter has sold and distributed every vial of Gammagard® S/D that it has produced each year. Working with the FDA last year, we sped up delivery of our therapeutics to caregivers and on to their patients. I want to state emphatically that we at Baxter are not stockpiling product and we never have stockpiled product, nor are we enabling others to do so. As was previously stated, virtually every one of our customers for Gammagard® S/D is on allocation. That is, they are getting only a specific amount of the product -- which is all we have to give them.

BAXTER'S RESPONSE TO THE SHORTAGE

Now, I want to elaborate on the efforts that we at Baxter have taken to increase the likelihood that patients who need our products can get them. As I have noted, a quick end is, unfortunately, not possible. Even if we could obtain and use increased quantities of plasma today, the sheer complexities of production, plus the extensive processing and testing, add up to a lag of at least seven months before finished protein therapies would reach patients. I would like to turn now to what Baxter has already done and will be doing in the future to improve product supply.

Immediate Steps Taken by Baxter

- We have established emergency allocation procedures to make sure that patients with acute conditions can get our products.

- We are limiting non-emergency orders from new customers while the product is in short supply and under allocation.

- To concentrate all our efforts on production, we have temporarily called a halt to *new* clinical research that would involve IVIG and reduce the available supply. Clinical research that is currently under way, of course, must continue. To jeopardize patients' welfare by altering their medical regimen would be unethical.

- To make certain that product reaches the end-user – the patient – more speedily, we have requested and obtained FDA permission to release some lots more quickly after production than previously, with no decrease in safety margins.

What Baxter is Doing Now

- To increase output, we have arranged for our recently acquired facility in Rochester, Michigan, to join our Los Angeles plant in processing an intermediate form of IVIG for final processing at other Baxter facilities. Once approved by the FDA, this should lead to an additional supply of 150,000 vials of IVIG in the United States in the latter half of 1998.

- Baxter's Immuno AG facility in Vienna, Austria, has long processed an IVIG therapeutic known as Endobulin®. It has been successfully used to treat thousands of patients outside the United States. We have applied for approval and supplied the FDA with supporting data to allow us to import this additional product so that U.S. patients can benefit. This should make an additional 75,000-150,000 vials available.

Baxter's Longer-Range Efforts

We have already indicated our intensive efforts to cope with the situation under discussion. We are committed to continued investment in technology to create synthetic proteins, for example,

and to our never-ending search for methods to maintain high product yields, eliminate waste and conserve our valuable resource -- human plasma.

OTHER SUGGESTIONS FOR MANAGING SUPPLY

Mr. Chairman, there are also some things that *others* can do to help address the current issues.

- Patients can encourage their families and their friends to become blood or plasma donors.

- In some cases, patients can educate themselves about alternative therapies and become less reliant on an IVIG product.

- Physicians, too, can continue to explore alternative therapies for the patient who currently uses an IVIG, or explore them for patients who are being given an IVIG for a non-indicated use.

- During the shortage, physicians should also continue efforts to allocate the product to the most needy cases. Additionally, they should monitor prophylactic use closely, with an aim to reduce the amount of product required.

- Lastly, the regulatory agencies and governing bodies have an important role. The FDA, the Centers for Disease Control (CDC), the NIH, and others must continue to work closely with the fractionators. The FDA should continue doing all it can to expedite the release of product lots and speedily investigate and approve new facilities, equipment, and procedures. The CDC should continue to monitor and determine the true nature of any public health threat that may affect the blood supply, and the NIH should continue to make available for development the new technologies and scientific advances that federal research and grants have supported.

Patients need a balanced, considered approach to product supply that involves no compromises on safety. In addition, we hope that quick action can be taken on our applications before the FDA to bring patients in this country a vitally needed and proven product.

PRIVATE MARKET IS EQUAL TO THE TASK

The current situation aptly illustrates that markets work. Once my company began to receive signals from the marketplace -- from hospitals seeking to place orders for additional product and from customers seeking new sources of supply, Baxter responded with the action plan I've outlined here to raise supply levels to meet the increased demand. The signals were first received in November of last year. Others responded as well. We expect the results of these responses will begin to be seen in the months just ahead.

CONCLUSION

In summary, let me reiterate to the Committee that we at Baxter remain committed to a policy of critical examination of all of the processes we use, to continuous improvement of these processes and our products, and to full and thoughtful consideration of suggested ideas and innovations from patients, doctors, the FDA and other governing bodies, and, of course, from Congress. A frank and open dialogue, we believe, can most effectively help us in our response to the scientific and medical challenges that confront us today.

In conclusion, let me say again that Baxter is committed to providing patients with the safest, highest-quality and most effective therapies. We are doing everything in our power to alleviate this shortage as quickly as possible.

Thank you, Mr. Chairman, for the opportunity to present our views today.

Mr. SHAYS. Thank you very much, Mr. Bacich, and I appreciate you being here.

We'll now go to you, Mr. Matveld.

Mr. MATVELD. Thank you.

Mr. SHAYS. Did I say your name properly? Is it Matveld?

Mr. MATVELD. Yes, it is. Thank you. Good afternoon, Chairman Shays, members of the subcommittee, ladies and gentlemen. I am Ed Matveld, president and CEO of Alpha Therapeutic Corp. I appreciate the opportunity to speak to you today about the availability of immune globulin intravenous, IGIV, and the many activities Alpha is undertaking to improve access for patients who depend upon this lifesaving medication. Alpha takes this situation very seriously, which is why I am here today.

Our roots as a plasma fractionator in Los Angeles, CA, began in 1948. Founded as Courtland Laboratories, the company was later part of Abbott Laboratories and in 1978 it was incorporated as Alpha Therapeutic Corp. Alpha is now a privately held company, ultimately owned by Yoshitomi Pharmaceutical Industries, Limited of Osaka, Japan. Nationwide, Alpha employs over 2,900 people. Today, Alpha prepares albumin and also coagulation factors to treat hemophilia. Alpha's IGIV product, Venoglobulin-S, is indicated for treatment of PID, primary immune deficiencies, ITP, a platelet deficiency, and Kawasaki's Disease. Alpha is now preparing a submission to the U.S. FDA for an intramuscular use of Venoglobulin-S to prevent the hepatitis A infection.

It is important to note that Alpha's production levels for IGIV have increased over the last 5 years. Our fractionation plant continues to operate at full capacity, 24 hours a day, 7 days a week. We are presently operating under a consent decree with the Justice Department and the FDA, and are very hopeful that the intense efforts to satisfy the consent decree will not require a production slowdown.

The removal of the FDA's lot release exemption for IGIV has added delays to an already lengthy manufacturing process. Now, documentation for each IGIV lot must be reviewed by the FDA. Up to 3 weeks may elapse before the product is released. However, the FDA has accelerated its reviews and most lots are released in 7 days or less.

As for off-label uses, Alpha believes that all treatment decisions are between the prescribing physician and the patient. Alpha does not promote usage of Venoglobulin outside prescribed, approved indications.

Alpha's production of IGIV continues to grow. Over the last 5 years, Alpha has increased its production of IGIV by about 100 percent and we forecast another increase for 1998 and future years.

Regarding exports, today's economy is a global one and diseases have no boundaries. We have committed to providing our products to patients on a worldwide basis. It would be irresponsible for us to ignore the needs of patients in other parts of the world. Alpha's IGIV is predominantly sold in the U.S. domestic market. Our international exports are very minimal. Reducing or eliminating this small level of exports will not have a significant effect on the U.S. market and will virtually eliminate access to lifesaving therapies in some countries.

Alpha has taken steps in late 1997 and early 1998 to get Venoglobulin into patients' hands more quickly. To accomplish this, we have redirected our distribution efforts. Now, 85 percent of our customers are direct accounts such as hospitals, physicians, and home care companies. This is up from the previous year number of 30 percent. Alpha's distribution actions have significantly shortened the time to provide product to the patient and in some cases by as much as 30 days.

As for pricing, each year since 1993, the domestic average selling price for Alpha's Venoglobulin-S rose very modestly. Inventory levels at Alpha over the last 5 years have been insignificant. The years 1993 and 1994 averaged about 26 kilograms of IGIV in inventory. In 1995, we had 37 kilograms in inventory. This was reduced to 1.5 kilograms in 1996, and 0.1 kilograms in 1997.

Our commitment to patients is evidenced by Alpha's investments in plasma production for the future. More than $20 million has been invested in product safety enhancements over the last 5 years. In that timeframe, Alpha has also invested all of its profits and an additional $33 million in facility upgrades and expansion. Another $75 million project is now under construction for additional facilities. Assuming no reduction in production lot size, we are planning to increase IGIV production by 40 to 50 percent by the year 2003.

Alpha Therapeutic Corp. is committed to providing high-quality, safe, and cost-effective products for improved patient care. With a 20-year history focusing solely on plasma products, we will continue to dedicate ourselves to these important therapies and the patients they benefit.

I thank you for inviting me to present this information, and hope that it has clarified the issue.

[The prepared statement of Mr. Matveld follows:]

Good morning Chairman Shays, members of the Subcommittee, Ladies and Gentlemen. I am Ed Matveld, President and CEO of Alpha Therapeutic Corporation. I appreciate the opportunity to speak to you today about the availability of immune globulin intravenous (IGIV) and the many activities Alpha is undertaking to improve access for patients who depend on this lifesaving medication. Alpha takes this situation very seriously, which is why I am here today. We have made every effort to provide as much IGIV as is possible.

I am here to share with you specific information about the efforts Alpha has taken to increase production of IGIV. Alpha has also reduced the length of the supply chain from fractionator to patient. I will address in general terms Alpha's pricing for IGIV and our products sold in the domestic and international markets. Alpha has made a very significant commitment in the past to facility enhancement and expansion and will continue to do so in the future. Finally, I will include estimated increases in IGIV production and will also describe our research efforts in immunoglobulins.

History of Alpha Therapeutic Corporation

Our roots as a plasma fractionator in Los Angeles, California began in 1948. Founded as Courtland Laboratories, the company was a pioneer in the development of the first coagulation factor product, Factor VIII. Courtland was later sold to Abbott Laboratories in 1968 and became the Abbott Scientific Products Division. In 1978, it was incorporated as Alpha Therapeutic Corporation. Alpha is now a privately held company, ultimately owned by Yoshitomi Pharmaceutical Industries, Ltd. of Osaka, Japan. This year, we are proud to celebrate our 20th anniversary as Alpha Therapeutic Corporation. Alpha is the largest pharmaceutical company in the city of Los Angeles and these roots extend to more than 50 plasma donor centers in 15 states. Nationwide, Alpha employs over 2,900 people.

Beginning with our roots in 1948, when Courtland processed albumin for the U.S. Army, the company has expanded into several plasma products. Today, Alpha also prepares coagulation factors with excellent efficacy and safety to treat hemophilia A and hemophilia B. Alpha's IGIV product, Venoglobulin®-S, has strong viral inactivation steps and is indicated for treatment of idiopathic thrombocytopenic purpura, Kawasaki disease and primary immune deficiencies. Alpha is preparing a submission to the U.S. Food and Drug Administration (FDA)

for intramuscular use of Venoglobulin®-S 10% solution to meet the needs of prophylaxis of hepatitis A infection.

All of our plasma products licensed by the FDA are processed at our fractionation plant in Los Angeles, from plasma collected by Alpha owned or contracted plasma donor centers throughout the United States. Only U.S. sourced plasma that has been tested by Alpha at our Memphis Testing Laboratory is brought into our fractionation plant.

In addition to all FDA required tests, Alpha currently tests all plasma donations for hepatitis C virus (HCV) using state-of-the-art Polymerase Chain Reaction (PCR) testing. In 1997, Alpha became the first U.S. fractionator to conduct a study on the utilization of PCR testing to detect the presence of the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in plasma donations. Alpha is an investigator under an Investigational New Drug Application (IND) sponsored by National Genetics Institute. Samples from all final product lots are also PCR tested for HCV, HIV, hepatitis A virus (HAV), and hepatitis B virus (HBV). This testing is an additional safety measure to gain added assurance that our plasma donation testing and processing steps are working to minimize the possibility of virus transmission.

Reasons for the IGIV Shortage

Information has been provided through the International Plasma Products Industry Association (IPPIA) regarding the industry-wide reasons for the shortage, all of which affect each fractionator in varying degrees.

I will address the efforts Alpha is making to deal with the shortage, however, it is important to note that Alpha has not had significant reductions in production levels now or in recent years. (Exhibit A) Alpha continues to operate at full capacity, 24 hours a day, seven days a week. We are presently operating under a Consent Decree with the Justice Department and the FDA, and are hopeful that the intense efforts to satisfy the Consent Decree will not require a production slowdown.

We were, however, directly affected by the withdrawal policy regarding Creutzfeldt-Jakob Disease (CJD). In our case, Alpha actually quarantined 334 kilograms of Venoglobulin®-S for three months and then, with FDA concurrence and special labeling, released it for sale in January to March, 1998. This quarantined product was unavailable to patients for just under six months.

Also, the removal of the FDA's lot release exemption for IGIV has played a part in further delaying an already lengthy manufacturing and product release

process. Now, documentation for each individual lot must be reviewed by the FDA before the product can be shipped to customers. Up to three weeks may elapse before product is released. However, the FDA has accelerated reviews and most lots are released within seven days.

Increased use has been cited as another reason for the shortage. While Alpha does not have specific data on this subject, we do know that there is now better diagnosis of primary immune disorders. As for "off label" uses, Alpha believes that all treatment decisions are between the prescribing physician and the patient. Alpha does not promote usage of Venoglobulin®-S outside prescribed, approved indications.

History of Alpha's IGIV Production

Alpha's production of IGIV continues to grow. Over the last five years, Alpha has increased its production of IGIV by 100% (Exhibit A) and we forecast another increase for 1998 and for future years.

The overall issue of capacity expansion is very complex. Alpha has increased its production by additional plasma throughput and by greater utilization of immune globulin proteins. In the last five years, Alpha has increased total plasma input by 12%. We have also increased the use of intermediate proteins from 44% to 84%. These increases have come primarily from expansion in the IGIV portion of our facilities and increases in production lot sizes.

History of Alpha's IGIV Sales Market

Why do we export product? As you are all aware, today's economy is a global one and diseases know no boundaries. We have committed to providing our products on a worldwide basis. It would be imprudent and even irresponsible for us to ignore the realities of the world economy and the needs of patients in other parts of the world. By spreading our sales over several countries' economies, we are able to manage the risk that a fluctuation in one market would have a drastic financial impact on the company. In terms of research and increased capacity, we are better able to finance these improvements when the costs are spread over a larger patient population.

As shown in Exhibit B, Alpha's IGIV is predominately sold in the U.S. Domestic Market. Our international sales exports have averaged 6% over the last five years. This small export percentage is because Alpha's foreign affiliate produces IGIV for the European market.

There are people who need IGIV everywhere. Alpha's relatively small exports benefit patients in U.S. Territories and foreign countries who need and deserve high quality and safe products. Reducing or eliminating this small level of exports will not have a significant effect on the U.S. market and will virtually eliminate availability of lifesaving therapies in some countries.

Recent Changes in Alpha's Sales Distribution Channels

Alpha took steps in late 1997 and early 1998 to get Venoglobulin®-S into patients' hands more quickly. Prior to that year, the economics of the IGIV market were slanted toward the indirect or wholesale market. Hospitals, pharmacies and home care companies (called direct accounts) preferred to purchase most of their IGIV from these distributors (indirect accounts), who provide a valuable inventory control service to their customers.

As noted in Exhibit C, Alpha has redirected its distribution efforts. This change from 30% direct sales to 85% direct sales has significantly shortened the time it takes the finished product to reach the patient.

Although this change in the distribution channel has resulted in increased customer administration and receivables costs for Alpha, we believe it will be beneficial to patients by reducing the time it takes to provide the product to them.

Alpha's distribution actions have significantly shortened the time to provide product to the patient by as much as 30 days in some situations.

Pricing of IGIV

Each year since 1993, the domestic Average Selling Price (ASP) for Alpha's Venoglobulin®-S rose modestly by about 4 percent. In 1997, Alpha's domestic ASP for IGIV rose by 14 percent. This increase was created primarily by added testing costs for improved product safety, the costs attendant to this change in distribution channels and other inflationary factors.

The new testing costs included the mandatory p24 antigen testing for HIV, which started in June, 1996. Additionally, Alpha began pioneering work in PCR testing of plasma donations and samples of final product lots, which I described earlier. While we are excited about the increased safety implications of PCR, the research investment by Alpha for developing an entirely new viral detection method for plasma is significant.

Additionally, Alpha has changed its distribution channel to sell more Venoglobulin®-S to direct customers. This change will help direct product to patients more quickly, but not without added costs. Where we previously sold in larger quantities to a smaller number of customers, we now sell to many individual hospitals and home care companies. This has more than doubled the actual number of customer accounts for which we maintain records, track orders, invoice and carry receivables.

Alpha has not made exorbitant increases in its selling price for IGIV. All increases have been tempered for inflationary trends and additional safety precautions for our IGIV product.

Inventory levels

There is a critical need for immune globulin by patients around the world and this need is growing. The amount of final container product Alpha had in inventory at year end over the last three years is insignificant. (Exhibit D) The years 1993 and 1994 averaged about 26 kilograms of IGIV in inventory. In 1995, we had 37 kilograms in inventory at year end. This was reduced to 1.5 kilograms in 1996 and 0.1 kilograms in 1997.

A review of the last six months of IGIV shipped and the amount in inventory available for distribution showed that we averaged 240 kilograms per month in sales and a little over 2 kilograms a month in inventory. This does not include the 335 kilograms of IGIV quarantined for three months, which were released during January through March of this year.

Alpha obviously has not held significant inventories out of the normal distribution system.

Increased Alpha Production in the Future

The ability to further increase production is affected by construction time, scientific aspects of manufacturing and the very necessary required regulatory review before new facilities are approved or production process changes can be implemented. As I mentioned earlier, Alpha is operating at full production capacity. While we would like to change our production capacity instantly to meet increased demand, this is a difficult task. Even slight changes in the process can have dramatic effects on the final product, including its efficacy and patient tolerance. Exhibit E show Alpha's production time line from plasma donation to final product.

First, increasing capacity is affected by the complex nature of the product. Immune globulin is a biological product derived from human blood plasma. Just as people are unique, each person's plasma has varying levels of antibodies. Our production process has been carefully engineered over the years to produce consistent results.

Secondly, the addition of new facilities or any changes in the production process must be tested, validated and completely reviewed and licensed by the FDA before they can be implemented. This is a necessary part of the process and one which protects the health of patients. I do not mention it as a deterrent to

facility expansion, but rather to explain why adding capacity takes time. We will continue to work closely with FDA to obtain the needed approval of our new facilities as I outlined previously.

The attached chart (Exhibit F) shows the short term time lines for the activities Alpha is implementing to increase IGIV product supply. There is not an easy answer or an immediate solution, but Alpha's dedicated employees will continue to work on solutions to increase supply to the patients who depend on us.

This commitment is evidenced by Alpha's investments in plasma production for the future. More than $20 million has been invested in product safety enhancements over the last five years. In that time frame, Alpha has invested all of its profits, plus an additional $33 million in facility upgrades and expansion. Another $75 million project is now under construction for additional facilities. Assuming no reduction in production lot size, we are planning to increase IGIV production by 40 to 50% by 2003.

Research in Immunoglobulins

Based on needs identified by physicians and patient groups, Alpha is conducting a number of research and development activities in immunoglobulins that include:

Research for additional indications:

Bone marrow transplant - prevention of graft vs. host disease

Severe steroid dependent asthma and atopic dermatitis

Studies for new products:

Immune globulin intramuscular (IGIM) - prophylaxis of hepatitis A infection

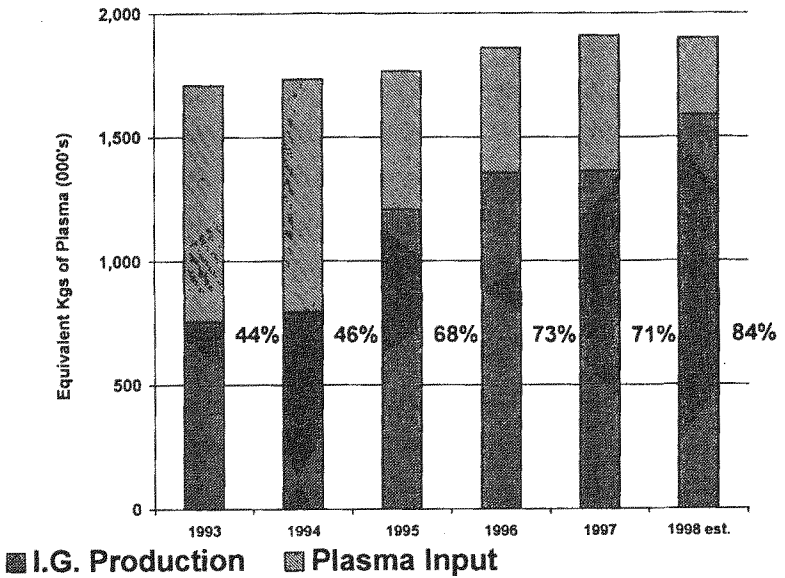
Patients depend on immune globulins for a variety of indications. Alpha is committed to studying the use of its immune globulin therapies and improving patient care worldwide.

Conclusion

Alpha Therapeutic Corporation is committed to providing high quality, safe and cost-effective products for improved patient care. With a 20 year history focusing solely on plasma products, we will continue to dedicate ourselves to these important therapies and the patients they benefit.

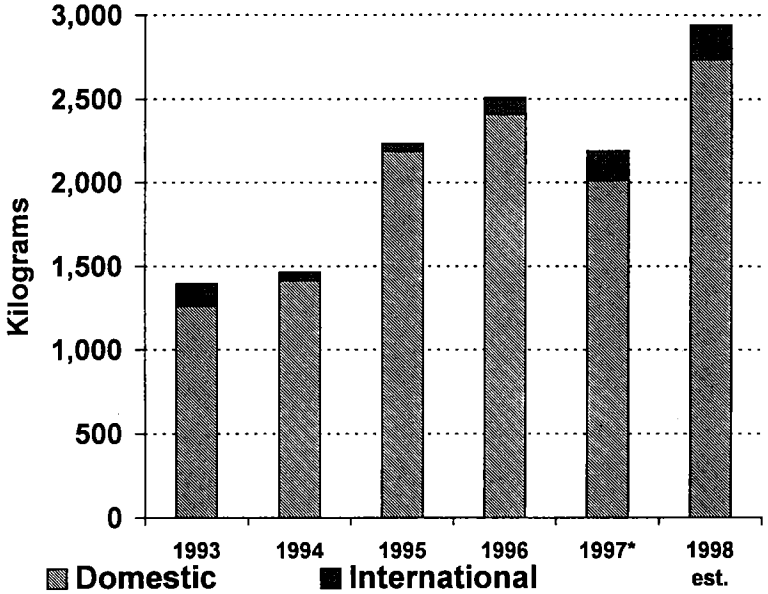
I thank you for inviting Alpha to present this information and hope that I have answered your questions.

Exhibit A
Alpha Therapeutic Corporation
Plasma Input & Plasma Used for Immune Globulin Production



alpha THERAPEUTIC CORPORATION

Exhibit B
Alpha Therapeutic Corporation
Immune Globulin Sales



*334.5 Kgs of IGIV was quarantined for 3 months and released for sale January through March 1998

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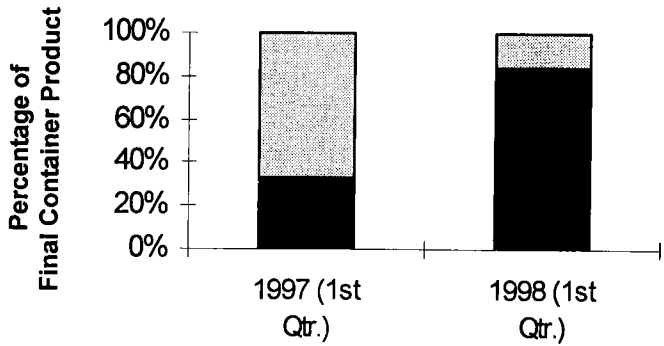
Exhibit C
Alpha Therapeutic Corporation
IGIV Distribution Pattern



In-Direct (Wholesalers)

Direct (Hospitals, Pharmacies, MDs, Home Care)

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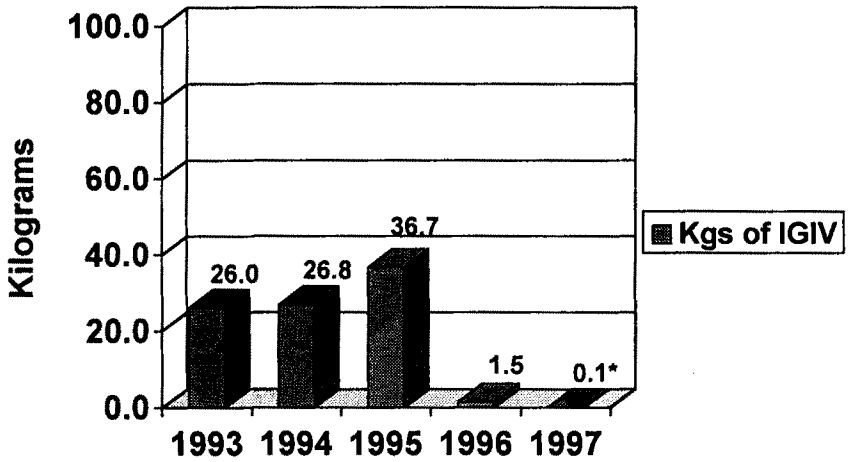
Exhibit D
Alpha Therapeutic Corporation
Year-End Final Product IGIV Inventories



*Excludes 334.5 Kgs of IGIV which was quarantined for 3 months and released for sale January through March 1998

alpha*

Exhibit E
Alpha Therapeutic Corporation
Production Timeline

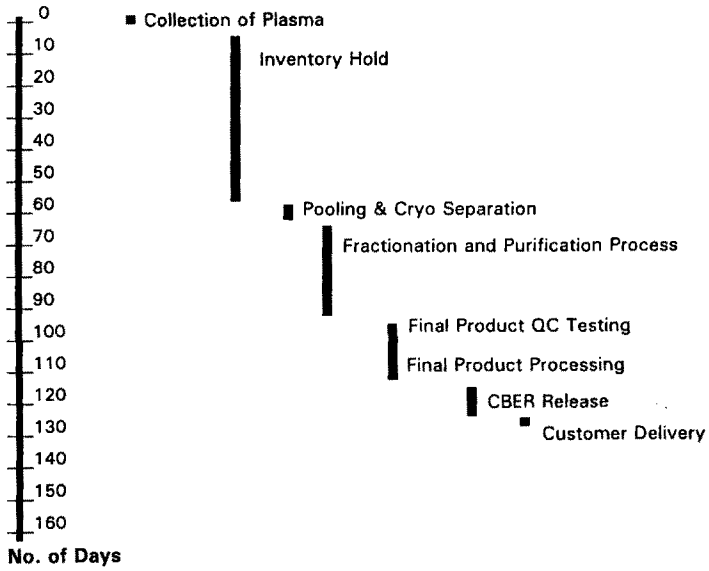


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Exhibit F
Alpha Therapeutic Corporation
Initiatives to Increase IGIV Supply

1998 Add 375 kgs of IGIV production from converted facilities

1999 Add 500 kgs of IGIV production from process modifications

2000 Add 500 kgs of IGIV production from new facilities

2003 Add 937 kgs from process enhancements and new facilities

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THERAPEUTIC CORPORATION

Mr. SHAYS. Thank you, Mr. Matveld. Let me allow Mr. Bult, Jan Bult, to just go through the chart, and then I'll start my questions after you have gone through it.

Mr. BULT. Thank you, Mr. Chairman. I would like to say right from the beginning what we have done. We had received the question from the subcommittee to provide you data on exports and pricing for the last 2 years. We felt it was extremely important to come up with additional information, especially since this issue is so important and we feel that transparency is extremely relevant and important to us.

What we have done is, we have shown here the total numbers, the aggregate data——

Mr. SHAYS. This is in your testimony as well, correct?

Mr. BULT. Yes, the table, the chart is in the testimony. But what we have done is we have provided the subcommittee with the company individual data so that the committee had a chance to verify the numbers. I think it's very important, but since it is proprietary information, that was the way we did it.

Let me walk you through the tables.

Mr. SHAYS. Let me be clear. The information that we have is proprietary information?

Mr. BULT. This is public information.

Mr. SHAYS. You have backed it up with proprietary information here?

Mr. BULT. That's correct, and you had a chance to verify these numbers.

Mr. SHAYS. Which is not available to the public, right?

Mr. BULT. Yes.

Mr. SHAYS. Yes. OK. Thank you.

Mr. BULT. What you see in the table on the right hand side, you see the numbers from 1996, 1997, and 1998. Let me start with the first line. What you see here is what is the total quantity of manufactured immunoglobulins for 1996 and 1997, and what is the forecast for 1998.

That does not necessarily mean that this quantity is available for the market because we have to deal with withdrawals and recalls. We heard about that this morning. And we had other technical operation problems that were reflected in the number that you see in the second line.

That leads to a total number of available supply, and the available supply was 13,752, as you can see. About 13,000 in 1997, and the forecast for this year is about similar. Those numbers now are divided in domestic supply and export numbers. So what you find here are the exact numbers for use within the States, and the quantity that was exported.

The other line which I think is very important is the inventory. You see that the inventory at the first of January 1996——

Mr. SHAYS. I missed what you said, I'm sorry. What is the next most?

Mr. BULT. Inventory.

Mr. SHAYS. Inventory, OK.

Mr. BULT. Yes. So the inventory at the first of January 1996, was close to 1,900 kilograms. Went down to close to 1,300 kilograms in

1997, and at this moment is below 800 kilograms, which is a clear indication that this industry is not stockpiling.

Within that inventory, the industry in response to an FDA request, has built up an emergency supply. In 1997, the minimum supply, the emergency supply available every day was 105 kilograms. For this year, it's increased to 430 kilograms, which is one of the measures of the industry to ensure the delivery to patients in critical need.

Another important question regards pricing. The only difference in this chart with the data that we have submitted to the subcommittee is that you find numbers here for 1996 and 1997. The average sales price in the State was $26.37 in 1996, and in 1997, it was $27.91. What we have done after our submission, we have further collected data for the first quarter of 1998, because we felt it was important for you to know what the current trend is. And we are happy to provide you with the company-specific information for verification purposes, as we've done before.

We feel it is extremely important to provide you with accurate information, because that's the only basis to have a very useful discussion. What we've done in the other chart is we divided the factors that affect the availability of immuno-globulin. And we have heard a lot with this supply demand. And if you look at the left hand side, in the supply, this covers the manufacturing quantity. It covers the withdrawals and recalls. And also it covers what was used from the inventory so far.

The blue boxes are factors that have an impact on the supply of immuno-globulins; however, these are issues that we cannot quantify. The green boxes are all the issues that we can quantify, and that's what we've done. And what I hope that you get from this picture is that, wherever possible, where we had an option to quantify the numbers, we have done it. This leads to transparency, and I think that's very important for today's meeting.

Mr. SHAYS. Thank you very much. Let me begin by having you comment on the export number that you have. It seems to me the export number, regardless of supply, is somewhat constant. In fact, the export went up from 1996 to 1998, it's projected. How can that happen if the supply is going down?

Mr. BULT. I think the first issue that we have to realize, Mr. Chairman, is that the numbers that you see here only reflect the numbers of the four IPPIA companies. It does not take into account the other manufacturers here in the State.

Mr. SHAYS. All right. I realize, but we're now playing by the same rules here.

Mr. BULT. OK.

Mr. SHAYS. If you're going to bring that before me, I want to respond to it.

Mr. BULT. Now the question about the export. As we have heard several times today.

Mr. SHAYS. Let me just be clear. I'm just focusing on this chart now.

Mr. BULT. Yes.

Mr. SHAYS. OK.

Mr. BULT. What we have heard today is that the shortage and the current problems we are facing occurred in late 1997, which

means that until fall 1997, everything was on track and there was no problem with any numbers. What you see with these numbers is the factual data for 1997. We have not broken this down into monthly data, so we have no indication what the trend was in 1997.

We feel it is very important to have an ongoing data gathering effort which tells us on a quarterly basis what the numbers are. And that will help us to better understand what the trend is and what the predictions are.

Mr. SHAYS. OK, but I'm going to respond to that. In 1996, your domestic supply was 11,400, and in 1997 the domestic supply was 10,331. Your export in 1996 was 2,352, and in 1997 it went up to 2,663. And I just need to understand why that number went up in export, and why the domestic number went down almost 1,000.

Mr. BULT. What I said before, Mr. Chairman, these are the factual numbers, and the shortages that we are referring to at this moment occurred late November. I think it's extremely important that we have a better understanding about what the trend is in these numbers and we can't give that analysis from these numbers. So I can't give you a precise answer on the reasons why. These are factual numbers.

Mr. SHAYS. Well, that's the reason why we're here today. So you're basically giving me a chart that you feel comfortable in telling me would be helpful, and the first thing I want to focus in on is not helpful. And then you're telling me the chart's irrelevant to that. You know, it makes it difficult for me to want to talk about the other issues. So when it doesn't support your thesis, you're telling me it's irrelevant, and when it supports your thesis, you're telling me it's relevant.

Ms. SCHULZE. May I make a comment?

Mr. SHAYS. Sure.

Ms. SCHULZE. That might help, or hope it will. Centeon last year had a drastically reduced supply, and we do very little export. So if you look at the 1997 versus 1996 domestic supply, it's low by at least 1,000 or 1,500 grams, just because of us. So if everybody else stayed the same—that alone could amount for that difference you're talking about.

Mr. SHAYS. Let me just say something. I'm not going to ask you what your individual export numbers are, but you all are under oath and you all have been very helpful, and this is going to be a good hearing. But I need to know from all the companies if your exports went up in 1997, and if your supply went down. That's the question. I don't need to know the amounts. If you want to tell me——

Ms. SCHULZE. Our supply went down drastically and exports went essentially to zero.

Mr. SHAYS. OK.

Mr. TUREK. Our supply went up, and our exports stayed the same.

Mr. BACICH. Our supply went down, and so did our exports.

Mr. MATVELD. Our supply went down and our exports rose minimally.

Mr. SHAYS. Mr. Matveld, percentage-wise, how much did your supplies go down? Let me do this. I don't need to know that. What

I need to know is whether you have fixed contracts overseas that you have to fulfill? Is there a certain level that you have produced? And I will ask each of the companies.

Mr. MATVELD. Is that directed at me, sir?

Mr. SHAYS. Yes, we'll start with you.

Mr. MATVELD. We do most of our distribution through a subsidiary in the Far East for IGIV, and they do have some contractual relationships. But the increase was minimal.

Mr. BACICH. I would say part of our exports are contract-based and some are not.

Ms. SCHULZE. Ours are—a very small percent are contracted.

Mr. TUREK. A significant component of our exports is Canada, which is a contract that we have, and in 1998 this may account for upwards to 40 percent of our exports. And we are a single supplier to the Canadian market, so we have a very strong commitment to our neighbors to the north to continue with this contract.

Mr. SHAYS. What I don't understand, and I bet most Americans don't. How much of the blood supply is purchased, and how much is basically donated, in terms of the blood that you get. In other words, one of the things we talked about is your capability to increase your production level, but it's obviously based on the amount of plasma that you get.

Mr. BULT. I think, Mr. Chairman, if I may respond to that question. It's very relevant to know what the real numbers are. I can tell you that the total number of collected plasma in the States for our members is around 11 million liters per year.

Mr. SHAYS. Eleven million what?

Mr. BULT. Liters.

Mr. SHAYS. Liters? OK.

Mr. BULT. Per year. I have to come back to you if my number is not correct, but my understanding is that for blood collection, it's about 3 million liters per year donated. But what is very important is to realize that what we're talking about today is a shortage in finished products.

Mr. SHAYS. OK. Can I put a request in? You have a message that you want to get across. I have questions that I need answers for.

Mr. TUREK. Let me try and answer it real quick for——

Mr. SHAYS. No, no, I just want to tell you what I think the rules should be. I'm going to ask the questions. I'm going to be very fair about giving a chance to answer the question. If in the end you think that you need to qualify and tell me that I have asked a dumb question or an irrelevant question, or that I'm not focused on what's pertinent you're free to do it. But I have something to my madness here, and I want to pursue it.

Mr. TUREK. Well, let me try and answer real quick for you, Congressman. The issue is not the plasma supply. The issue is the manufacturing capability of the facilities. We are able to procure plasma at a rate that is equal to whatever manufacturing capability the facilities have in the United States. So therefore, the rate-limiting step is not the amount of plasma that one can procure or collect. It's really whether the facilities can manufacture more.

Mr. SHAYS. OK, and I appreciate that. And so, bear with me here. I need to understand why that's the case. When you periodically hear there's a shortage in the blood supply, is that just whole

blood where there's a shortage? Is it because you can store plasma so we don't have shortages? What makes for the lack of shortage in plasma, if we don't have a shortage?

Mr. BACICH. Mr. Chairman, may I respond to that? And you drew the right distinction. You do have to talk about whole blood and plasma. In the case of whole blood, that plasma is also fractionated, and that's the plasma that is generally collected, for the most part, by the American Red Cross. And I think you know Baxter fractionates their plasma.

The rest of the volume that Mr. Bult talked about is source plasma that is collected by the manufacturers, either in plasma centers that they own or in plasma centers that they contract with. So, coming back to focus in on how that impacts on the shortage, there is adequate raw material. Today, we don't have adequate conversion facilities to convert plasma. In fact, may I add one more point?

Mr. SHAYS. Sure.

Mr. BACICH. In my opening comments, I talked about our evolution of capacity taking about 12 years, because I think you've heard everyone say how complex these facilities are and some of your staff has visited facilities.

The shortage was precipitous. It happened in a very short timeframe. So the response of adding capacity back, if that's what's required, can't be equally as precipitous. So that's why we're sitting here with this short-term shortage.

Mr. SHAYS. I understand. I understand that obviously there's going to be some set of time on production. I also understand that if all five companies decide to increase their production levels too much, you may have even, potentially, an oversupply.

Mr. BACICH. Yes.

Mr. SHAYS. So I understand that you want us to look at all these factors. I just want to start with the basics, and you all know them and you are comfortable, but I don't. So I want them on the record.

So when Americans hear that there's a shortage and a need for blood, it is not in any way related to your operations?

Mr. BACICH. It is not. It's generally referring to the formed elements.

Mr. SHAYS. And, again, the total amount is 11 million liters for your member companies?

Mr. BULT. The total amount collected in the United States for manufacturing purposes is 11 million liters.

Mr. SHAYS. And how much for your membership here? I just need to know——

Mr. TUREK. Individually, we can answer I suppose. We collect approximately 2 million liters.

Mr. SCHULZE. And our number is very similar.

Mr. BACICH. The same ball park.

Mr. MATVELD. Two point five million liters.

Mr. SHAYS. So when we're talking about this, we're 9.5, around there.

Mr. BULT. Yes, and the difference is by individual collection centers who will also provide plasma to the fractionators, but the companies we're referring to, own collection practices.

Mr. SHAYS. OK. Well, I'm sorry, I didn't quite understand that. Are you saying that others collect and add to their production level?

Mr. BULT. We are not adding to production level, but to the United States, a total collection of plasma for manufacturing purposes, 11 million liters. The companies have individual collection centers, but beyond that, there are other collections centers that also collect plasma.

Mr. SHAYS. Right, and do those collection centers, then provide the plasma to the companies before——

Mr. BULT. Well, we have to realize that a lot of this plasma goes overseas, and it's used to, for example, in Europe to manufacture products there, products overseas.

Mr. SHAYS. Yes. Did you understand my question? Can you respond to it?

Mr. TUREK. Basically, we respond in terms of what amount of plasma we collect for utilization in our facility, and there's an additional amount that is collected, that is then purchased by other companies. For example——

Mr. SHAYS. But not your companies?

Mr. TUREK. Sometimes it's our—it's the affiliate companies of companies who have facilities in Europe, as well.

Mr. SHAYS. OK. Now who is providing for Canada in a significant way? Mr. Turek, do you get plasma from Canadians as well, and is that——

Mr. TUREK. Yes. We get approximately 150,000 to 180,000 liters on an annual basis of Canadian plasma that is then fractionated in our facility in North Carolina.

Mr. SHAYS. OK. And they're a population of what, about 28 million?

Mr. TUREK. Twenty-six million.

Mr. SHAYS. OK, thank you. So one thing I can feel comfortable about is that production is the challenge; it's not the raw material?

Mr. TUREK. Correct, yes.

Mr. SHAYS. I'm going to go to a different line of questioning, but why don't I give Mr. Snowbarger the floor, and I'll come back.

Mr. SNOWBARGER. Thank you, Mr. Chairman. I guess I ought to start out with the question that I indicated I'd be asking all of you, and that is: I presume, at least, that you are constantly doing research about how products that you currently have or maybe slight variations of them, can be used basically to increase market. I mean, you're doing it to address problems, but for business as well. You're doing it to increase market for your products, and if you could just comment on these expanded uses, the off-label uses, the expanded-label uses, and how much effort you are putting into that versus increased production capacity. Like I mentioned before, it appears that you're creating a larger and larger market with a finite capacity to deal with that.

Mr. TUREK. If I can go first.

Ms. SNOWBARGER. Go ahead, please.

Mr. TUREK. There, we're investing in both areas, both in research, and in what we call technology, to increase the output as well.

From a research standpoint, we have been instrumental in getting the approval here for bone marrow transplant, and for the use in pediatric AIDS here in the United States. We've also done research in Japan to get Kawasaki disease approved as an indication, and we're currently doing studies in the area of multiple sclerosis for the hope of also getting IVIG approved in multiple sclerosis in the future.

Now, having said that, simultaneously, as I said in my comments, since 1994, we've been planning, and putting in place plans to improve our ability to have more IVIG available. This is why we have purchased a facility now in Europe that we are upgrading, and we are also constructing a new facility in North Carolina; and those two combined will increase our output by approximately 50 percent, in terms of product specifically for IVIG.

So, we're trying to marry both together in terms of increasing our own output, and ensuring that the proper documented studies performed that will support the utilization of IVIG and those indications.

Ms. SCHULZE. In our case, we have very limited money right now being spent on the research side. We have one study on hold because we have no product, and that's Gillian Barre for children. We've had to cancel several others because of the shortage, and our own issues—seven or eight other trials that we had started. And we have with the FDA a submission to get an expanded indication for ITP, but that work was done some time ago. So in our case, we're focusing on production.

Mr. BACICH. Mr. Snowbarger, in fact, my team this week is working on our 10-year strategic plan, and it's addressing two of the key issues that you raised, and that is: what are the things that we can do to improve vials, and that is to get more IGIV out of a liter of plasma today, and to do that safely and in full compliance; and, the other two pieces is to really get our antenna out there, and try to understand what are the 10-year needs.

And in those 10 years, what do we need to do in terms of capacity? What do we need to do in terms of yield? What do we need to do in terms of new features to existing products, or perhaps, new intravenous gamma globulins. One other thing, I think you know that Baxter did in the last few years was to acquire the Immuno Corp., which was of great value to us for a couple of reasons.

One, is they had great strength in R&D, great leadership in terms of safety, but also, that it added a tremendous amount of capacity which allowed us to import some product back. So, we're trying to deal strategically, with all the issues that you asked about.

Mr. MATVELD. Yes, Mr. Snowbarger, we have an application that we'll be submitting very soon on bone marrow transplantation. It's a wind-down. The project is basically completed.

We also are in process of wrapping-up another project for the IGIM, the intramuscular, and that is in its late stages. So, we have very little activity at the present time on R&D for IGIV, aside from, we are gearing-up very strongly for a new production process. As we've stated to you, the mechanics of increasing capacity is very difficult.

Our first new production increment will come as a result of adding a new facility. The second piece will come from a minor process

modification. The big change that we want to make which will bring us about a 25 percent yield increase overall, cannot be done until we have a new facility. It means going in, and changing all of the equipment in the process, and so forth. If we did that in the old environment, we would further exacerbate the shortage that we're into now. So, we have to be patient and wait until the new facility is completed to get that extra big yield bang.

Mr. SNOWBARGER. I think some comment was made that you're probably not likely to recover all these capital costs, at least in the near term. Is that the same for all the companies?

Mr. TUREK. Yes.

Mr. SNOWBARGER. Let me go to a different line of questioning, if I could.

To some extent or another, it's my impression that you're all international firms, and that you either have market outside the United States, you may have production outside the United States, is that—let me ask the question specifically? How many of you have manufacturing processes outside the United States?

Mr. MATVELD. For our company or affiliated companies?

Mr. SNOWBARGER. And he's asking a good question. I would say, affiliated companies, I think.

Mr. TUREK. Then you would mean, currently operating?

Mr. SNOWBARGER. Yes.

Mr. SHAYS. So, how many respond in the affirmative? We had, for the record, three out of four.

Mr. SNOWBARGER. Three out of four, with Bayer being——

Mr. TUREK. Bayer, as I mentioned. Our sole manufacturing facility is here in the United States. We have recently purchased a facility in Italy, and this is not in operation.

Mr. SNOWBARGER. It's not operating yet. Right. My question is this, and it comes from one of our people in the audience who came up between panels, and it sparked an interest for me in what kind of regulatory environment you find in these other countries where you're doing business? How that compares? And how that affects your ability to produce? And the reason for my question is this: the comment was, there's not a shortage in the world anywhere except, the United States. Now, that may—I don't know the accuracy of that or not, but, at least his indication was that through his internet searches, and things of that nature, other countries aren't having this problem.

And so, if you've got some insight on why we might be having the problem, and other countries aren't, I'd appreciate that.

Mr. BULT. If I could start on that issue, Mr. Snowbarger. First of all, whole manufacturers, whether this is in the United States or in Europe, let's take that as an example, they manufacture under the current regulatory systems in place, and I think that that's obvious.

The second question is why and is there any difference in the shortage problem in the United States or other parts of the world?

I think one very important element is that we have seen over the past, and you heard it this morning from other witnesses, occasionally, shortages happening. And in those cases, industry was always able to respond to that particular situation. I think one important element is that here, in the United States, you have a very well-

established diagnosis and treatment system. My feeling is, and that's what I hear from patient groups, for example, is that many patients in Europe are still undiagnosed. And it may well be that if we look at the number of diagnosed patients that will have a significant impact.

Mr. SNOWBARGER. Anyone else?

Ms. SCHULZE. Just a perspective. In Europe, there's far more capacity in general, for fractionation. And a lot of the countries have their own quasi-political government relationships where they produce a lot more. So really, there's a lot more supply than demand than in this country. Just a completely different system.

On top of it, you have different regulatory requirements, some more stringent, some less; it really varies a lot, country-by-country, agency-by-agency.

Mr. TUREK. But, just to add to that, if you have a facility in Europe, and you want to import in the United States, you must get FDA approval for that. Let's be clear on that.

Mr. SNOWBARGER. Oh, I understand that. I'll be honest with you. My question goes to the lengths, I mean, this is a balance again, between the quality of the product, and the quantity. And apparently, the quantity problem is different in Europe and other countries. I don't have any idea what the quality situation is, and whether they have made a decision to counter-balance in favor of quantity versus—and I'm not talking about major differences in quality, I'm talking about minor things, and perhaps, intervention in the production process that slows down our process or makes it more costly.

Mr. BACICH. I was just going to add, that I agree with what's been said, but you also ask the question that I think is asking about, what is the difference of inspection technique or inspection rigor as you look around the world? And I think all of the participants today will tell you that since we do distribute our products worldwide, of course, we're inspected by foreign agencies.

In addition, I have operations around the world, and I can tell you that there are different approaches. There are different emphasis. But all countries take quality and safety very seriously, but perhaps, they take different approaches to how they inspect facilities, and how they license those facilities. But I don't think it's inspection rigor that is driving the key shortage we see today. With all the factors we've talked about, I still come back to the precipitous drop in capacity that has fostered most of it.

May I ask one question, maybe out of order, to the chairman. Can I come up there and get one of those pitchers of water. I'm sitting here with a dry mouth and I just keep staring at it? [Laughter.]

Mr. SHAYS. You mean to tell me, we have all those pitchers up there, and none of them have water.

Mr. BACICH. Actually, I thought you were just torturing us.

Mr. SHAYS. We're just trying to teach you to deal with shortages. [Laughter.]

Mr. BACICH. I promise you, I'll just take a sip. [Laughter.]

Mr. SHAYS. Would you fill up the other pitcher too? OK, thanks. Thank you. I'm very sorry.

It's a great question, though, and a good answer, too.

Mr. SNOWBARGER. Mr. Chairman, one more line of questioning that came from, I think, the panel that just proceeded this, maybe it was the other one; and that is, relationship between the productions facilities, and the distribution mechanisms that we have for this. To what extent, do you have some input into where these products are distributed? Are you ready and willing to sell to any willing buyer? Is there the potential out there that we have little men who could—I won't say they are—but, could horde a product that because of limited manufacturing capacity, could create a false shortage for a profit? That's kind of all one question even though it was asked in a series.

Mr. MATVELD. May I address that one? I covered that partially, in my presentation. I think basically, aside from existing contractual relationships, we have the opportunity to direct the product where we wish.

Alpha, during the past year changed from a 30 percent direct distribution, meaning the hospitals, the pharmacies, and the home-care companies to 85 percent. And that resulted in approximately, a 30-day improvement in getting the product to the patients. So we feel there is an opportunity there, and it was as a result of changing markets. We took advantage of it to try to and get the product out there, and abate the problem.

Mr. BACICH. The question that you asked, I think is a useful one, and that is what is the process that we go through to try to decide how to satisfy demand? And it's similar to what you've heard from the others. Well over 90 percent of our product, either goes to home-care companies or direct users of the product.

But this also helps answer the question that I heard earlier this morning. What about vial size? And why is 10 gram in one place or 5 gram in another, and how is that really directed and who really controls that?

The customer controls that. The customer always controls that. The processes that we use today are really very sophisticated, and——

Mr. SHAYS. Could I just ask, when you say that though, if the product is in such short supply, do they have the ability to get one vial size or the other?

Mr. BACICH. I was going to get to that.

Mr. SHAYS. OK.

Mr. BACICH. On the front-end of our system, it starts with global demand planning. And in that global demand plan, it decides where the products going to go, and it decides in which configuration will it be used. In a time of shortage like this, it's very possible that that gets out of balance, so that perhaps you may have more 10-gram than 5-gram.

So, I think what you'll see, Mr. Chairman, is as we start to fill this shortage, you're also going to see the choices of products being filled, and so, you won't have to have a customer buying 10, when they really need 5.

Mr. TUREK. If I can just add to that as well, most of us, and I know from Bayer's standpoint, we have eight different sizes; 50-ml, 20-ml, 100-ml, 250. And so, it really comes down to the person administering at the end, whether they are being thoughtful, and whether they are ensuring that they are not wasting it, because

many of the doses require multiple vials. They wouldn't just use a 50-ml vial. They may use a 200, and then a 50, and so on.

So, the onus is really on the treater, in the end to ensure that the wastage is minimized. We provide the options very clearly, with the number of vial sizes that hopefully gives them that flexibility that will minimize any wastage.

Mr. SNOWBARGER. Mr. Chairman, you were very generous with time. I appreciate it.

Mr. SHAYS. Thank you. Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me begin by first saying I thank all of the witnesses for your comments and I'm happy to hear in terms of this whole thing about packaging, because that was a big discussion earlier, this morning. And also, to say that to Bayer, I do really know a lot about your outreach program and want to let you know that we appreciate some things that you're doing, especially in the minority communities around this Nation, so I just want to say that before I go to the questions. [Laughter.]

On a serious note, what could the industry do to have an emergency supply? What could be done to have an emergency supply? What could we do, you do, I should say?

Mr. TUREK. Well, if I can begin. We've now allocated approximately 25 to 30 percent of our available product for the United States for emergency supply uses. And we've targeted it into three areas: the first area is the Pediatric AIDS patients, a very important group of patients; second, is in association with the Immune Deficiency Foundation, we have a relationship with them to ensure that their patients who have a very great need of getting a regular allocation of product; and, third, we set aside an emergency supply on a monthly basis that can be utilized for other emergencies that may occur on a ongoing basis.

Mr. TOWNS. Yes, down the line.

Ms. SCHULZE. For us, you're asking the question of what can be done? In our case, it would require more general production. Right now, we're producing so little and releasing so little, our current contracts, and there's penalties if you don't supply the contracts, eat up virtually everything.

So despite that, we set aside 5,000-grams a month, and we go through a process and allocate that. But frankly, until we get the releases coming out, and the product coming out, we can't increase it dramatically.

Mr. TOWNS. I'd be delighted to yield to Mr. Chairman.

Mr. SHAYS. When you say your contracts, are some of them with distributors or do they——

Ms. SCHULZE. No, we don't have any contracts with distributors. When I say that VHA, for example, they've contracted——

Mr. SHAYS. The answer to the question is no, you don't have any distributors. Thank you.

Ms. SCHULZE. No.

Mr. BACICH. Mr. Towns, I testified earlier that we have increased our emergency——

Mr. TOWNS. I apologize because I was pulled out a couple—so maybe you've discussed it.

Mr. BACICH. I'd be happy to answer your question. We've increased our emergency supply to 14 days. So, as long as we keep replenishing it, it would stay there. Now, in addition, I also mentioned that we are importing products in an emergency IND from our European operations to add to that. And also, one of the operations that we acquired from Immuno, we have a licensed application with the FDA right now, that can add upwards of another 150,000 vials this year. So, we think we'll be able to continually add to that throughout the rest of 1998.

Mr. TOWNS. Thank you.

Mr. MATVELD. At Alpha, we isolate approximately 10,000 vials per month. We use a service company that takes the order, and we sell no more than in 100-gram increments. We replenish the inventory every month, and in conversations with my sales and marketing group the other day, we have not turned down any orders that have come through that vehicle on the emergency basis.

Mr. TOWNS. Thank you.

Mr. BULT. I think there's no need for me to come up with a company-specific response, since I represent the association.

Mr. TOWNS. Yes, that's correct. Earlier today, there was some discussion about profiteering. Can each member of the panel tell me the percentage difference in the average price charged for your product 2 years ago, and the price charged today?

Mr. TUREK. Could you repeat the question? Do you mean the price increase? Is that the question?

Mr. TOWNS. Yes. You know, much of the discussion about profiteering, was centered around middle-men or middle-women or brokers? That's what I want to know, in terms of——

Mr. BULT. Sorry, I was a little-bit disrupted, but let me try to catch-up with your question. What I understood that you asked whether there was any variation in the price-range the last 2 years?

Mr. TOWNS. Right.

Mr. BULT. We have provided the aggregate numbers which you can see here on this chart.

[Chart shown.]

Mr. BULT. We have provided to companies, specific data, to the committee for verification purposes. So, you have that data available, but since it's—the increase in 1996–1997—we just have to do the math—I think it's about 5.8 percent. And the increase, we have to be careful because you're comparing a quarter to an annual number is about 13 percent, as you can see in the second column.

Mr. TUREK. Yes, and our increases are in lines with those increases that Jan mentioned on an aggregate basis.

Ms. SCHULZE. Ours, too.

Mr. TOWNS. What about the overall medical costs, how does that compare? Overall medical costs?

Ms. SCHULZE. To who?

Mr. TOWNS. Increases, I'm talking about.

Ms. SCHULZE. You mean, production costs?

Mr. TOWNS. Yes.

Ms. SCHULZE. Production costs, at least for us, has gone up far more than twice the price increase, far more.

Mr. TUREK. The same for us.

Mr. BACICH. Our costs have increased significantly over these last 2 years, but our product costs which is in these averages, is about the same that it was in 1994—price.

Mr. MATVELD. Our costs have gone up some. Part of it has been as a result of mandated P–24, HIV antigen-testing by the FDA. Second, as another safety effort, we have implemented PCR-testing for HIV and HCV and that has added significant dollars as well. Third, we have increased costs in our new method of distribution because we're dealing with a lot more customers out there by going directly to them. And there are modest inflationary increases.

We are not finished with the Consent Decree yet, and I, at this time, cannot estimate the significance of those dollars.

Mr. TOWNS. Right. And I'm going to leave this open for you. If you don't want to answer it, I'm not going to press the issue. I mean, I'm really not. I'm going to yield back, if you really don't want to deal with it. In some cases, I understand that several of the companies have purchased products on the open market in order to fulfill previous commitments. I want to know if any of you, any of the companies here would be willing to talk about that today?

Ms. SCHULZE. I can talk about that. As part of the same contract I just referenced, it's called a "must-take-but-must-supply" type of contract.

Mr. TOWNS. Right.

Ms. SCHULZE. We recently re-signed it. But at the time of last year, we were obligated to provide a certain number of grams every month whether or not we had it. Obviously, when that contract was first signed we thought we would have plenty of production. What we were obligated to do is go basically on the same open market and, at whatever price we could get, provide that product to the customer at the contracted price. And that added-up very significantly.

Mr. TOWNS. So you lost money on it, really.

Ms. SCHULZE. Lots of money.

Mr. TUREK. And I can add to that as well, Mr. Towns. With our contract with Canada, we have such a thing called a cost-differential. In other words, if we're unable to supply, they go out on the open market and purchase it, and we pay the difference in terms of what our contract is with them, and what they end up purchasing it on the open market. And that, of course, causes us to lose money versus what we normally would have done.

Mr. BACICH. Mr. Towns, I just want to make sure I understood your question. Is your question, are we, is it to the earlier question I heard about forcing people to commit to contracts?

Mr. TOWNS. Right.

Mr. BACICH. OK. No, we are not doing that.

Mr. MATVELD. Alpha is also not purchasing product made by other manufacturers to satisfy contracts or commitments, we are not.

Mr. TOWNS. OK, thank you very much. Mr. Chairman, I yield back.

Mr. SHAYS. Thank you. I'm trying to understand why everyone didn't anticipate the increase demand. Why your own company didn't, and why your competition didn't? And if there are reasons,

I just don't know what they are. What would have been the reasons for——

Ms. SCHULZE. Talking to me?

Mr. SHAYS. All right. We're going to start with each one of the four here.

Mr. BACICH. I'll be able to start with this one. As I mentioned in the opening comments, I think we were adequately anticipating demand up to the precipitous changes. As I mentioned to you, it's taken 12 years to get from where we started to where we are today, anticipating the demand. But when you take as significant a bite out of the supply as some of my colleagues talked about earlier, the response time with the nature of these processes, you simply won't be able to catch up quickly.

Mr. SHAYS. With all due respect, I understand that some of the shortages because of some recalls and so on are at a minimum amount, frankly. The question I'm asking is whether that is not withstanding? There is an increase demand. You all know that you've got to increase your production capability, but how come it happened now, rather than before and why wasn't your strategic planning people able to see that?

Mr. BACICH. My point is——

Mr. SHAYS. I mean, you make a good profit that people need.

Mr. BACICH. Absolutely, my point is that if these shortages didn't happen, I heard one manufacturer off the marketplace for several months, I heard another at 50 percent of capacity. Our IGIV through-put was hit by as high as 30 percent for periods of time. And if we would have added those vials back, and then look at our strategic plan in the capacity that we plan to add for the future, I don't think we'd be sitting here talking about the shortage today.

Mr. TUREK. If I could just add to that, Mr. Shays. We began planning to increase our capacity back in 1994. OK. And that means that you have to put scientists in place to look at how you can improve your technology, get capital approved in your company, begin construction, validation of that facility, and then, final licensure.

And I can tell you in our facility, that means by the year 2001 or 2002, even though we started back in 1994. But it's not as if, at least in my company, we haven't been anticipating it. It just takes a very long time from the science to the output of a product before that can occur.

Mr. SHAYS. There are basically three factors that we agree on. We agree that increased demand contributed to the shortage. We agree on decreased production, and we also agree on the availability of finished products, after withdrawals or recalls to address the risk of transmitting CJD. Now, that last one was the minor one. The major one was the reduction in production because you had to re-evaluate your safety procedures.

Between those last two, we acknowledge that increased demand is there. So, of those two, you're basically saying to me, Ms. Schulze, for instance, that your plant wasn't operating in a way that could satisfy you or FDA, and that you could produce a product that was safe enough to meet everybody's standards.

So, your production levels fell by how much?

Ms. SCHULZE. Seventy percent.

Mr. SHAYS. For how long?

Ms. SCHULZE. Well, we were not producing for the first 6 months of 1997, any IVIG. And then when we began production, it was a gradual ramp-up.

Mr. SHAYS. Was that a miscalculation? That was a pretty long time, longer than FDA anticipated.

Ms. SCHULZE. Right. I think it was longer than we anticipated, either.

Mr. SHAYS. Let me ask this question. This has helped me in the way I ask the next question. What was your production level, each of you in terms of 100 percent, were you operating over the year during 1997, at 80 percent of capacity, at—let's go down.

Mr. TUREK. We were operating at about 100 percent capacity in 1997.

Ms. SCHULZE. And we were roughly 30 percent.

Mr. BACICH. I'd say, 75 percent in 1997.

Mr. MATVELD. We were 100 percent.

Mr. SHAYS. What I'm also gathering is that we're at a fine line between production meeting supply or not. Even if you had been at full production, we still would have been at the margin, slightly over, but at the margin.

Mr. BACICH. If I may respond to that. If we were at 100 percent, we would have been able to meet our customers needs. And of course, that shortage continues well into 1998, and from the comments I heard this morning, I think there was a question about why, these voluntary apparent shutdowns beyond what's really required? And I think the answer to that is, and someone has talked about the issue of validation, and in many cases, validating a piece of equipment, means that you can't do it while you're manufacturing the product. You have to do it in some other way to take physical measurements or biological testing. So, the only way you can validate that piece of equipment is to take it out of operation.

Or in some cases, the only way to really adequately train people is to train them while they're not manufacturing the product. So, that was really the only way we could accomplish these changes.

Mr. SHAYS. That's a very valid point, and I'm happy you made it. But, the question I still want to ask is, whether we were still operating within the margins. In other words, all of you knew that you were pretty close to capacity; you could fulfill all your orders, and it was likely you all knew you could run at 100 percent capacity. Correct? You would sell everything you made. That's an indication to me that when you're running at 100 percent capacity, you've got opportunities. And this is a business, and you do make money.

Mr. BACICH. I can address that. As I mentioned, as we're looking at our 10-year strategic plan, one thing that we're looking at is, what will we need to add in terms of capacity to run on a permanent basis at 85 percent capacity, for example. I don't know if that's where the actual number will come out. That, then, gives you some discretionary capacity of whatever it might be, the balance. It allows you to deal with the market opportunities that you talked about or, in this case, an emergency.

And with the increase in costs in this business, managing cycle time, managing inventory turns, managing inventories to their

most sensible level, is in everybody's best interest. That helps us manage cost to the customer.

But I think the answer is longer-term, is to have facilities where you have discretionary capacity so that if some disaster happens, it's an easy matter to simply use your un-utilized capacity, and that's how we're looking at it for the future.

Mr. SHAYS. I would think that would almost be a no-brainer, in our dialog. And I'd be happy to ask Mr. Bult, if he wants to respond. But, it would seem to me that since you make a lifesaving product, and if there are shortages, that the companies have an obligation to be able, as an aggregate, to meet supply even when there are going to be some plants that are going to have to stop operations for a while. I don't know if you want to respond to it.

Mr. BULT. I think it's a very valid point, Mr. Chairman. However, I would like to stress that up to November 1997, we were able to supply in enough quantity. So, you are right that we were operating on the edge, but up to November 1997, we were on track.

Mr. SHAYS. Let's just take 1995, then. Mr. Turek, were you at 100 percent capacity?

Mr. TUREK. We were very close to 100 percent.

Mr. SHAYS. Ms. Schulze?

Ms. SCHULZE. Yes.

Mr. BACICH. Yes.

Mr. MATVELD. Yes.

Mr. SHAYS. Well, with all due respect, if you're at 100 percent capacity in 1995, I think the point still stands.

Mr. MATVELD. Chairman Shays, excuse me, may I add a comment. I think I've pointed out in our presentation that Alpha has increased its capacity 100 percent over the last 5 years. So, running at 100 percent capacity was an increasing number.

Mr. SHAYS. Let me let all of you make that point because I think that's valid. Your production since 1995 has gone up what?

Mr. MATVELD. 100 percent.

Mr. SHAYS. OK, let's go down the line.

Mr. BACICH. Increase from 1993, excuse me.

Mr. SHAYS. 1993?

Mr. BACICH. In the last 5 years. Increase from 1993 is probably about 30 percent for us, but let me make one other comment. As I talked about our evolution of capacity which has taken about 12 years, we anticipated the demand with each addition of capacity. And through that 12 year period, we never experienced a shortage like this. This is the first time I think this industry has ever faced a shortage of this nature. So we do have to do something different, and I think everyone's prepared to do that.

Ms. SCHULZE. I'm not certain of the numbers, but my expectation would be that we were basically the same capacity. One thing I think we need to understand here is, at least for Centeon, we produce a number of life-saving therapies, all of them, in fact. There are tradeoffs among them. So, I would say it's not necessarily a no-brainer that we would invest, because that's really what this is, an incremental capacity on a certain product-line, as opposed to say, hemophilia. So, I think our capacity is really pretty flat.

Mr. SHAYS. But you raise another point. If it's not a no-brainer for you, it's got to be for us. And then the government's going to have to step in.

Ms. SCHULZE. Well.

Mr. SHAYS. No, just let me make my point. My point is that you're saying that you have lots of different products, and the market's going to help dictate where you go. You're going to make that micro-decision, but someone's got to look at the macro. And so, we're going to look at the macro.

Ms. SCHULZE. That's valid, yes.

Mr. SHAYS. Mr. Turek.

Mr. TUREK. We've probably grown about 20, 25 percent since 1995, but if you're looking for solutions, and I think that's what you're looking for——

Mr. SHAYS. I'm looking for solutions, and I'm looking for the proper role of Government in an industry that has a life-saving product. We could have had this hearing of all the people you help, but they would also describe the fact that they've gone through hell in the last few years. I need to know where the Government's responsible. I need to know where you are responsible collectively, that there not was a pre-meditated effort to do this, but that ultimately this is what happened.

Mr. TUREK. Well, unequivocally, I can say it was not a pre-meditated effort. I think that should go on the record.

Mr. BACICH. Mr. Chairman, may I make one other comment?

Mr. SHAYS. Yes, go ahead.

Mr. BACICH. I heard that discussion this morning. I fully appreciate what your job is as you try to understand all the causes, and then, try to understand what the fixes are. But, from the nature of the discussion I heard this morning, it sounds like you are pointing more at Government intervention than any other solution. And I invite you to point at us. Challenge us to fix it, not—there certainly is a key and important and integral-role for the Government to challenge us.

Mr. SHAYS. Right. That's what the purpose of this hearing is. It is to challenge you, and to challenge us as well. But, I will get to this last point. Before I do, I need to know what is the role, and I'm going to have you go down that list, but I don't want to ask that question right yet.

I want to get into two other areas. One area I want to get into is, how is it possible for Centeon to buy a vast sum of this product, when a hospital may not have been able to buy that vast sum? What did you have that the hospital didn't have? Where did you go in the market to buy it?

Ms. SCHULZE. All over the place. The same places they could go to. It's you know, literally picking up the phone, calling, finding who has it. So, I can't answer you. It seems they should be able to find it.

Mr. SHAYS. I make an assumption that you had to pay a top dollar for it?

Ms. SCHULZE. Yes.

Mr. SHAYS. Did you buy it directly from these other companies here?

Ms. SCHULZE. At the table, you mean?

Mr. SHAYS. Yes.

Ms. SCHULZE. I don't know.

Mr. SHAYS. You're under oath, and——

Ms. SCHULZE. I really don't know. I would tell you if I did. I don't know.

Mr. SHAYS. If a company, if Centeon came to any of the other three companies here, and said, "We have to buy a large amount," would you have provided that amount to them, and would you have charged greater than your basic rate to the hospitals, and so on?

Mr. MATVELD. May I answer that? We have a basic policy to develop long-term, longstanding customers. We probably would not have been in a position to be able to respond to their request.

Mr. BACICH. It would be the same position for Baxter.

Mr. TUREK. The same for Bayer.

Mr. SHAYS. So basically, you went into the open marketplace worldwide?

Ms. SCHULZE. United States only.

Mr. SHAYS. Why wouldn't you have gone worldwide?

Ms. SCHULZE. Well, the products aren't licensed. You need to have a license.

Mr. SHAYS. You'd have a gigantic problem with that. Let me understand about the middle-man in this issue. We have testimony, admittedly, just from one source, but that there are some middlemen that were charging higher prices. What is your practice with middle-men? During this time—and then, I'd like to know what you did about it—were you aware that any middle-man that you sold to was taking advantage of this, and increasing the rate significantly?

Maybe we can start with you, Mr. Matveld.

Mr. MATVELD. I'm not aware of that practice by any of our distributors. Had we known that, we would have discontinued any supply to them.

Mr. BACICH. Mr. Chairman, I believe our people testified at HHS that we distributed about 2 percent of our product through these distributors that you talk about, and I'm not aware of any of them abusing price, as you mentioned.

Mr. SHAYS. Do you feel that it's your obligation to periodically check to see? Do you have a system that would protect you and the public from that?

Mr. BACICH. I'm not sure that we do, but if I knew of it, I would certainly stop it.

Mr. SHAYS. OK.

Mr. BACICH. But, that's something that I will commit to you that I'll followup on.

Mr. SHAYS. Thank you, very much.

Ms. SCHULZE. We use distributors very little, as well. I'm also not aware of any of that type of pricing. Similarly, we don't have a system to ensure it. We would make the same commitment as Mr. Bacich just did.

Mr. TUREK. Yes, we use distributors really in two areas. One area is to work with Immune Deficiency Foundation, and the other area is for physicians office-use, for home-infusion or office-infusion to help keep healthcare costs down. But, we're not aware of any distributors. If we were, we would take whatever action necessary,

which is whatever is permissible by law to stop that from happening.

Mr. SHAYS. Let me say, I'm going to give all of you an opportunity to make any general points you want to make, since you may have this pinned-up desire to do that. But let me ask you. I thought, Mr. Friedman provided a nice vehicle for me to pursue this question. And that was, he listed six, and then we added one about questions that the FDA does not get involved in. And questions of where should they, if they focused on any, where their biggest focus should be on? And you may not say none, but I'd like you to tell me where, if any, it would be. How much to produce was one question. How much to charge? Where it is distributed? How it is exported? How much is stockpiled? The amount of off-label use? And the vial size?

I'll give it to you again. How much is produced? If they don't get involved, how much is charged? Where it is distributed? How it is exported? How much is stockpiled? The amount of off-label use? And the vial size?

Dr. Satcher said that if he had a focus on how he would deal with this issue, it would be mostly the amount of the off-label use. Since, he said, it's such a gigantic number, 50 to 70 percent, and the vial size. That's where his focus would be. He didn't say to what extent. And CDC said how much is produced, and I think, excuse me, how much is stockpiled.

Since, they come from that point, would any of you be willing to just jump in first on this issue?

Mr. TUREK. Yes, I'll jump in. That's not a problem. I think you know, and I don't want to do like Friedman in terms of saying it's a complicated question. But if you're asking for a ranking, very simply——

Mr. SHAYS. Let me just say, I believe it's a complicated question. And I don't believe that you're saying that the government should do it. I'm just saying, if they did——

Mr. TUREK. I would say that government together with industry, and treaters, really could——

Mr. SHAYS. And treaters?

Mr. TUREK. And treaters, physicians, could really work together on looking at rational use, which is this off-label issue. But what I would call rational use. I think that's really one area that could be examined together, as looking for rational use. In fact, it's also a very complicated issue, and some hospitals have attempted to do this themselves. But I would say that would be the first area.

The second area, if I had to choose one, I wouldn't call it exports. I'd turn it to the other way, and I'd call it imports. What methods are there to encourage more free trade between our partners in Europe and the United States that gives the greater flexibility to companies like the ones sitting at this table, to bring in product that is registered in other markets, into the United States? To allow us to go through, to weather these type of storms that we're——

Mr. SHAYS. You say, during times of emergency?

Mr. TUREK. For example.

Mr. SHAYS. OK, and basically, we're talking about similar products made overseas, but simply not licensed to be sold?

Mr. TUREK. Yes.

Mr. SHAYS. OK. In times of emergency. Define an emergency?

Mr. TUREK. Or even for long-term registration purposes as well. Probably, a two-step approach, for example.

Mr. SHAYS. OK. You added one to my list, but that's all right. Ms. Schulze.

Ms. SCHULZE. I would tend to agree with Mr. Turek that the off-label use is an important issue. Now, as an industry, I don't know quite what we can do about that. I would think HHS could get with physician groups. There's some role that could be played here.

And the other one, even though I would not invite it, but if there truly was an emergency reservoir that the country decides they need, maybe there's a way that we can get at that. You know, like the Department of Defense may do for whatever emergencies they think they have. But, if you collectively did that on a national basis, and the government became the purchaser, that might help.

Mr. SHAYS. Mr. Bacich.

Mr. BACICH. Thank you. I must admit, I found that discussion a little troubling this morning. Particularly, on the issue of what is the role, because I haven't been in this business for 30 years. The Food and Drug Cosmetic Act is pretty clear about what the role of FDA is, and what our responsibilities are, and it pretty clearly spells that out. So, for asking the question, what else can we do——

Mr. SHAYS. Let me ask you. In that role, as described, so should we never re-examine roles?

Mr. BACICH. No, not at all. But the nature of the discussion was one that it sounded like that wasn't clear.

Mr. SHAYS. What isn't clear? Make it clear to me.

Mr. BACICH. Well, as I sat here, and listened to the FDA trying to explain to you what their role is, I thought, that has been established for many, many years.

Mr. SHAYS. Right.

Mr. BACICH. I'm not suggesting that not to challenge it, but——

Mr. SHAYS. But I don't understand why you would even mention it. It's been established for many years, and they do some things well, some things not well, and some things we look at their role and say, it's too much. They regulate 25 percent of our lives. We know that. But we constantly have to re-evaluate. I mean, you do that in your company. Why shouldn't we do it in government?

Mr. BACICH. I don't disagree with that. But my point was, no one went back to the primer of what the basis is, and it sounded like there were no ground rules, and no perimeter. As though we were starting all over. Challenging the status-quo——

Mr. SHAYS. Let me just say to you that this committee has had many hearings on what their role is. I just wanted to know what their role wasn't. I could have had them spend time asking what their role was.

Mr. BACICH. All right, thank you.

Mr. SHAYS. OK.

Mr. BACICH. But the points that I would like to address. I think on the issue of off-label use, that's one, that I think is extremely important. Because as I listened to the discussions, sometimes it is as though off-label use is almost something that's frivolous or not needed. Yet, when I talk with physicians, both treaters in our busi-

ness, and outside of our business, what I find out is that off-label use is also life-saving, and tremendous life-improvement. So, it's not a waste of product. It's an appropriate use of product. But we need to think about how we do that for the future.

On the second point, that I believe Mr. Turek mentioned, and this is something that we're doing right now, and this is working on that emergency IND to bring European product here. That is clearly, one area that I think we need to look at; Not on the short-term basis, but on the very, very long-term basis. That products that meet the criteria of safety, no matter where they come from, should be able to be used here. And I think we're just starting to scratch the surface with that. So, that's got to be an area that we dig into.

Mr. SHAYS. OK, make that last point again, please?

Mr. BACICH. Sorry.

Mr. SHAYS. Just make that last point again.

Mr. BACICH. Yes, the last point is, to give you an example. We're working on bringing a product from our European operations, which is IGIV, to be used in the United States on an emergency basis. And so, we're working through a process, and I must admit, I don't understand all of it, but it's an emergency IND, and we're going through the last discussions now defining what I believe are called the inclusions and exclusions. And this will help tremendously in the short-term, but how can we pursue that as a long-term source of product? That is, we certainly don't want to back on safety or efficacy or anything like that. But I think there's got to be a path that allows us to bring safe and efficacious products here for Americans to use.

Mr. SHAYS. Well, it seems logical to me, if we export overseas, and we can guarantee the product is viable, and so on, as effective and safe, we would want to pursue that.

Mr. BACICH. Exactly.

Mr. SHAYS. I think that's helpful as well. Thank you. Matveld.

Mr. MATVELD. I think a point that Mr. Bult has made before and that is on the industry's willingness for a communication on an ongoing-basis, perhaps on a quarterly basis, sharing data with the FDA so we are all working off the same ground, and can understand that together.

I think rational use is another opportunity for us to make some progress, but perhaps, a little more difficult when we're talking bringing the physicians into that.

Something very concrete, I think, that could help us would be a focus by the FDA on our request for new facility approvals. We have some that will be coming up in the future, and typically, the periods of time can range from 6 months to 2 years for an approval. With a focus from the FDA, perhaps, we can do better on that, and bring more product to market a lot sooner.

Mr. SHAYS. Well, if you need to increase your production capability, and this equipment has already been basically approved, it's a matter of——

Mr. MATVELD. I'm talking a new facility, added equipment.

Mr. SHAYS. Added equipment, but we're not talking new technology.

Mr. MATVELD. No, not in this one.

Mr. SHAYS. We're talking about basically——

Mr. MATVELD. The current process.

Mr. SHAYS. An extension of what you have.

Mr. MATVELD. Yes, and that takes a long time.

Mr. SHAYS. Has that been a problem for any of you besides——

Mr. MATVELD. We have accepted the timeframes from the FDA in the past. I think in time of a national crisis like we're talking, it might be wise to address that, and see if there's an opportunity to get a focus from the FDA.

Mr. SHAYS. OK. Well, let me do this.

Yes, sir?

Mr. BULT. Chairman Shays, I would like to respond very briefly. I think we should not forget that the first responsibility of FDA is, of course, safety first. And that together with the compliance issue, we shouldn't forget that that is a primary responsibility.

I would like to come to import, which was mentioned by some of the other witnesses, because the further, I would say, use of import opportunities is a very important issue. But, we should not forget that we have already, a lot of products coming into this country.

Mr. SHAYS. We have a what? I'm sorry.

Mr. BULT. We have a lot of products coming into this country. If you look at the suppliers at this moment, not all companies are sitting at this table. In the next panel, we have other manufacturers. But let me be very, very precise on that. If you look at the supply from Novartis as a company, the products that come into this market they are equal to the number that our members are exporting. So, we should not forget there is a huge quantity coming into this country. So there's a balanced situation.

I think regarding the numbers, I think what Mr. Matveld said, is extremely important. We have committed to this ongoing data-gathering effort, and to publish that on a quarterly basis. That will help us understand what's going on. That is very important.

Mr. SHAYS. OK, thank you. Mr. Bult, go ahead. And in his last word, why don't all of you take that opportunity as well.

Mr. TUREK. I think——

Mr. SHAYS. In other words, let me just say. In terms of what you want to make sure you leave this committee with, the point you want to leave this committee with.

Mr. TUREK. Well, I think we've had a real opportunity to express, I believe, from their standpoint that we do take responsibility for our actions, and that we really want to address the shortage. And I think you've heard us talk about making sure we have emergency supplies available to those who need it the most. But I think, that's really the solution that we just talked about are probably the most important ones as we look forward in terms of looking at ways of ensuring appropriate use, so that we are making sure that it's not just off-label use. We have appropriate use of IGIV, and that we look at ways of ensuring that additional products can enter the United States that will afford a greater variety of opportunity to handle the shortages when they occur.

Ms. SCHULZE. I guess two things. One, I hope everybody now understands, that clearly, although we were a big part, you might say, the key part of the shortage in 1997, there was absolutely

nothing intentional about it. It's not something we're proud of. It's something we're recovering from as fast as we can.

And the second point is, 1998 is looking very good, and I think we'll be able to fully recover, and that will help us all.

Mr. SHAYS. Let me just quickly ask you, your production level now is at what level?

Ms. SCHULZE. That's not a simple question.

Mr. SHAYS. Approximately, give or take.

Ms. SCHULZE. Let me say, 50 to 60 percent.

Mr. SHAYS. And will you be up to full capacity next year?

Ms. SCHULZE. This year we will be. Each quarter, month-by-month, is much better.

Mr. BACICH. I must admit, I'm overwhelmed by this opportunity. After 30 years, I've got about a minute to say what I want. [Laughter.]

Mr. SHAYS. Yes, with all due respect, Mr. Bacich, I've noticed that you've taken advantage of saying—[laughter.] I know how you became president. [Laughter.]

Mr. BACICH. I guess this is the way I would summarize it. I think whether you're directing the activities, or the investigations, or whatever you do next, safety has to be No. 1. It just has to be. I think for someone like me who has lived through the HIV disaster that we had in our country, it's got to be safety. Safety, No. 1. And we certainly accept that, and I think that has to be the same for the regulators and the scientists that we challenge in this industry.

Two others. I think to ask for the expediting licensing for reasonable changes, whether they be emergency supply or a different way to bring product into the country, or as we're trying to add capacity in the United States, we're not asking to cut corners, but these kinds of changes should absolutely be at the top of the stack today. Those are the ones that will make the most difference.

And I guess the last one, I invite you to challenge us. And that is, I'm concerned about—I understand your probing and pushing and trying to understand what best can government do, but when it comes back to the actions, I try to urge you not to look for government intervention, but come back to us, and point your finger at us, and say, fix it. We would accept that.

Mr. SHAYS. Mr. Matveld.

Mr. MATVELD. I hope today, that we have clarified the situation on industry's role and responsibilities through the shortage. We've been very frank with all our data, and plan to continue on that basis.

I think what you've heard from everyone here, that there are plans for the future longer-term to address the shortage. There is expansion, from everyone going through. In the short-term, I think we've also heard that there will be some recovery of production from some people. And that recovery will also bring some short-term benefits.

We look forward to working closely to identify any opportunities that we can participate in to help alleviate the shortage.

Mr. SHAYS. I thank all of you. I do think you have reported yourselves very well. I think you have helped inform this committee. I do think this committee has a reputation of not looking for a Gov-

ernment solution, but we do believe that some of our biggest successes has been to highlight problems in hearings, and encourage regulators to be a little more forceful without too much intervention. And, we will be pursuing this. I invite you to continue to communicate with our staff, and I will output one request. I was going to ask questions about your 800-number. I'd invite each of you to call your own 800-number, and be a patient who needs a drug, and decide whether you think that 800-number is as helpful as you think it is. In three instances, and we'll respond in a letter to you, we found that the question of exclusive contract arose in a few instances, and I'd invite you to think in terms of how you deal with that on an 800-number.

We're going to recess. I think this has been a very helpful and candid panel, and I really appreciate you being here. We'll recess until this vote is done, and then, we'll finish up with the last panel. Thank you, very much.

[Recess.]

Mr. SHAYS. I call this subcommittee to order. We have before us Brian McDonough, CEO and responsible head, American Red Cross, Biomedical Services, Dr. Ruedi E. Wager, CEO, ZLB Central Laboratory, and Wayne Yetter, president/CEO, Novartis Pharmaceuticals, accompanied by, I'm sorry, Dr. Deborah Dunsire. Thank you.

You're all standing, if you'd raise your right arm please.

[Witnesses sworn.]

Mr. SHAYS. Let me say, for the record that you probably were here for a good part of the day and heard testimony from others. I'm happy to have your testimony put in the record. I think that you've seen how it's flowed, and I'm happy to have you address what you heard. I'm not going to be asking too many other questions than the kind of questions I asked. So in one sense, a lot of people have left, and you had to spend a long time here, but the other sense is, you have the opportunity to get the last word in. You kind of get the last impression on the committee.

I also want to say to you that on this committee, we do our homework. We will be issuing some kind of report or recommendation after we've had more time to digest this, and to potentially have another hearing. Or we may, in fact, decide that we can do this through dialog with the departments, and with the industry, and see the improvements taking place by dialog without the need for reports. So, we're somewhat flexible, but I found this hearing today to be very interesting. We will begin, I think, with you, Dr. Wager. I know you have a plane to catch, and we'll let you start us out.

Dr. WAGER. That's correct, Mr. Chairman.

STATEMENTS OF RUEDI E. WAGER, Ph.D., CEO, ZLB CENTRAL LABORATORY, BLOOD TRANSFUSION SERVICE, SWISS RED CROSS; BRIAN McDONOUGH, CEO, AMERICAN RED CROSS BIOMEDICAL SERVICES; AND WAYNE P. YETTER, PRESIDENT/CEO, NOVARTIS CORP., ACCOMPANIED BY DR. DEBORAH DUNSIRE, VICE PRESIDENT, ONCOLOGY BUSINESS GROUP

Mr. WAGER. Mr. Chairman, members of the subcommittee, I would like to thank the subcommittee very much for the opportunity to present today on the current shortage of immune globulin in the United States.

My name is Ruedi Wager, and I am ZLB's president and CEO, actually.

ZLB Central Laboratory is a non-profit organization. It's a foundation of the Swiss Red Cross, and focuses on research, development and manufacturing of plasma products, exclusively manufactured from blood donations of voluntary, non-remunerated donors. Our manufacturing plant in Switzerland has an overall capacity of some 1.5 mioliters of plasma equivalents, and the most important products manufactured are human albumin and intravenous immune globin. For both these products, we have a product and establishment license with the FDA.

Whereas our products are distributed in Switzerland by ZLB, different partners distribute our products outside Switzerland under a marketing and distribution agreement. Since many year, ZLB maintains an important relationship with the United States. In 1996, 1997, and 1998, ZLB bought and buys respectively on the average 900,000 liters of recovered plasma from American Red Cross, and other non-profit organizations, mostly community-based blood centers. It produces on the average 20 tons of albumin, and more than 3 tons of IGIV from this plasma. One hundred percent of the albumin manufactured from U.S. plasma is shipped back to the United States where it is distributed by different partners.

In the following, I would like to focus on the situation with IGIV. First, related to the causes of current and chronic shortage, I would not like to comment any further because all the reasons have been mentioned. However, I would like to mention here that there is an important issue related to the shortage of IVIG in the market, namely the speed of expansion, and the adaptation of facilities, because all these expansion and adaptations need approval by the FDA which lasts at least, 6 to 12 months. Let me elaborate a little bit on the actual situation of the shortage from ZLB's perspective.

As mentioned, during the years 1996 through 1998, ZLB bought through contacts with U.S. suppliers 900,000 liters of plasma equivalents as recovered plasma or paste intermediates. At no time ZLB maintained any significant stocks of plasma or manufactured IGIV. All finished goods are delivered immediately after release to our distributor in the United States, Novartis Pharmaceuticals Corp. Due to the complexity and long duration of the manufacturing cycle, intermediates are stored between the individual steps of the manufacturing process. These intermediates guarantee the continuity in our manufacturing operation which runs actually 7 days a week, 24 hours in all critical areas. At the end of 1997, our stocks of plasma and intermediates from the United States corresponded

to 800 kilogram IGIV, but as I said we had no finished goods of IGIV available.

I would like to mention the effective deliveries of IGIV to the United States, always compared with the maximum capacity and the total U.S. plasma available at ZLB. Our shipment to the United States in 1996 was 65 percent of that capacity in plasma. It increased in 1997 to 70 percent, and it will be higher than 80 percent in 1998.

ZLB was not aware of an existing or forthcoming IGIV shortage on the U.S. market until fall 1997. After having learned about the shortage, ZLB increased its efforts to supply IGIV from U.S. plasma to the United States market. In the first 4 months of 1998, more than 50 percent of the total amount of the 1997 supply was delivered to the U.S. market.

Continuing this effort, we will be able to deliver in 1998, 25 percent more IGIV to the U.S. market provided that the contracted plasma from the United States will be available to ZLB. This figure corresponds to 88 percent of the maximum capacity manufacturing capacity from U.S. plasma.

I would like to illustrate a little bit the discrepancy between the maximum capacity and the effective delivery to the U.S. market in 1997. As I mentioned, in 1997, 70 percent of the IGIV manufactured from U.S. plasma was effectively shipped back to the distributor in the United States. Approximately, 8 kilograms of IGIV were returned from the market at a later stage due to CJD.

In addition to the amount of IGIV delivered to our customers in the United States, 7 percent of the maximum capacity had to be destroyed as finished goods or intermediates before the products could be released and shipped to U.S. market.

Due to the fact that significant amounts of IGIV manufactured by ZLB had to be withdrawn and to be destroyed later, ZLB decided to adapt its manufacturing processes to reduce the potential risks related to CJD. Through these measures, 1997, additional 6 percent of the maximum manufacturing capacity was lost.

These two facts were responsible for a reduced IGIV output for the United States. Overall, 1997, 17 percent of the maximum available capacity for IGIV from United States plasma was shipped to European markets.

I would like to comment on the prices very briefly. ZLB supplies all IGIV to our worldwide distributor which is Novartis Pharmaceuticals Corp. at an ex-factory price which is established in our marketing and distribution agreement. Basically, there is one single ex-factory price for all IGIV supplies worldwide. However, the price for the shipments to Novartis did not change over the last 2 years.

Let me make the last comment related to the status of efforts to increase production and manufacturing at ZLB. The present capacity of ZLB to manufacture IGIV is, as I said, fully exploited. That means, certainly more than 95 percent of the capacity. In critical bottleneck areas, manufacturing operations run 7 days a week during 24 hours.

Since the yield of IGIV is compared with our competitors, already at a very high level, further improvement of this yield will be difficult to achieve. Despite these facts, ZLB already made and will

continue to make every effort to contribute to the elimination of the IGIV shortage in the United States.

In agreement with our distribution partner, ZLB is prepared to ship all IGIV manufactured from U.S. plasma back to the U.S. market. In fact, in the first 4 months, 1998, all the IGIV manufactured from U.S. plasma was delivered to the U.S. market, and we will continue during the shortage in the future as well.

Based on the increased delivery of IGIV in the first quarter, 1998, we are confident to ship 1998, 25 percent more products to our distributor in the United States. Under consideration of our past experience, additional 13 percent of IGIV manufactured will get lost due to withdrawals with respect to CJD, and preventive measures to keep these withdrawals at a minimum. Implementation of pool size, however, will further reduce the IGIV output at ZLB.

ZLB already started a significant investment in the expansion of the manufacturing capacity for albumin and IGIV 2 years ago. In fact, we increased our capacity over the last 4 years by more than 50 percent. The benefit of this investment will depend on the time to approval for the new equipment, and the shut-down period necessary most likely 1999, to make some important adaptations in our infrastructure.

I thank you for your attention.

[The prepared statement of Mr. Wager follows:]

Presentation to the Subcommittee of the House of Representatives on the Public Health and Public Policy Implications of Current Shortages of Intravenous Immune Globulin (IGIV)

Dr. Ruedi E. Wäger, President and CEO, ZLB Central Laboratory BTS SRC, Switzerland

I would like to thank the Subcommittee for the opportunity to present today on the current shortage of immune globulin.

My name is Ruedi Wäger and I am ZLB's President and CEO.

ZLB Central Laboratory BTS SRC is a non-profit foundation of the Swiss Red Cross and focuses on Research, Development and Manufacturing of high quality and safety blood plasma products manufactured exclusively from blood donations of voluntary, non-remunerated donors. Our manufacturing plant in Switzerland has an overall capacity of some 1,5 Mio liters of plasma equivalents. The most important products manufactured are human albumin and intravenous immune globulin (IGIV).

Whereas our products are distributed in Switzerland by ZLB, different partners distribute our products outside Switzerland under a marketing and distribution agreement. Since many years ZLB maintains an important relationship with the United States. In 1996 through 1998, ZLB bought/ buys on the average 900'000 liters of recovered plasma from ARC, other non-profit organizations (mostly community-based blood centers) and Baxter in the form of plasma or paste (intermediates manufactured from human plasma). It produces on the average 20 tons of albumin and more than 3 tons of IGIV from this plasma. One hundred percent (100%) of the albumin manufactured from U.S. plasma is shipped back to the United States where it is distributed by different partners.

In the following, I would like to focus on the situation of IGIV.

Causes of Current and Chronic Shortage

Regretfully, we had to learn about the shortages of IGIV by late fall of 1997. The causes may be as follows:

- the increasing demand and use of IGIV for an increasing number of indications/ therapies
- the increasing efforts of all manufacturers of blood plasma products to implement the highest standards regarding safety and quality of their products. To ensure full compliance with cGMP regulations, shut-downs in the manufacturing operations for maintenance, (re-) validation and adaptations are necessary.

- the adaptation and/ or expansion of manufacturing infrastructure need approval by the relevant authorities. Approval time lasts 6 - 12 months.
- the limited availability of plasma and paste
- the higher risk of recovered plasma and paste respecting withdrawal due to CJD of blood donors
- the quarantine of plasma and intermediates due to post-donation information which leads to manufacturing breaks and re-scheduling
- the efforts of blood product manufacturers to achieve highest level of scrutiny of documentation before product release to avoid recalls and withdrawals.

Actual Situation from ZLB's Perspective

As mentioned above, during the years 1996 through 1998, ZLB bought/ buys through contracts with U.S. suppliers 900'000 liters of plasma equivalents as recovered plasma or paste (intermediates from recovered plasma) on an annual basis. **At no time ZLB maintained any significant stocks of plasma or manufactured IGIV**. All finished goods are delivered immediately after release to our distributor in the United States (Novartis Pharmaceuticals Corporation). Due to the complexity and long duration of the manufacturing process, intermediates are stored between the individual steps of the manufacturing process. These intermediates guarantee the continuity in our manufacturing operation (7 days a week, 24 hours), if plasma is not available due to late shipments, post-donation information or quarantine (e.g. look-backs, etc.). At the end of 1997 our stocks of plasma and intermediates from the United States corresponded to 800 kg IGIV.

The effective deliveries to the United States market were - **in terms of percentage theoretical/ maximum yield** as follows.

1996 65% of the theoretical yield from 900'000 liters of plasma/ paste
1997 70% of the theoretical yield from 900'000 liters of plasma/ paste
1998 >80% of the theoretical yield from 900'000 liters of plasma/ paste

ZLB was not aware of an existing or forthcoming IGIV shortage on the U.S. market until late fall 1997.

After having learned about this shortage, ZLB increased its efforts to supply IGIV to the U.S. market. In the first quarter of 1998 38% of the original annual manufacturing amount budgeted for 1998 was delivered to the U.S. market. Continuing this effort, we will be able to deliver in 1998 **26% more IGIV to the U.S. market** provided that the contracted plasma from the U.S. will be available to ZLB. This figure corresponds to 88% of the theoretical yield.

Discrepancy Between Theoretical Yield and Effective Delivery of IGIV to the U.S. Market

1997, 70% of the IGIV manufactured from U.S. plasma was effectively shipped back to our distributor in the United States. However, approximately 8 kg of IGIV were returned from the market at a later stage due to CJD.
In addition to the amount of IGIV delivered to our customers in the United States, **7% of the theoretical yield had to be destroyed (as finished goods or intermediates) before release to our customers due to CJD** product withdrawals.

Due to the fact that significant amounts of IGIV manufactured by ZLB had to be withdrawn and to be destroyed later, ZLB decided to adapt its manufacturing processes to avoid part of the potential risks. Through these measures, 1997, **additional 6% of theoretical yield was lost**.

Considering the effective shipments to the U.S. market and the amount of products lost due to CJD (withdrawals and preventive measures in manufacturing), 83% of the total U.S. plasma available was manufactured into IGIV for the patient needs in the U.S.

Since our lyophilizers are the most important bottleneck in manufacturing IGIV, ZLB installed and validated 2 additional freeze-dryers in 1996/1997. The validation was completed by August 1997 and the documentation was sent to the FDA by October 1997. However, both lyophilizers cannot yet be used for the manufacturing of IGIV for the U.S. market. IGIV lyophilized in this new equipment complies to regulations outside the U.S.

Following a GMP inspection by FDA in November 1996, ZLB had to re-validate the 8 older lyophilizers.

These two facts were responsible for a reduced IGIV output for the U.S.
Overall, 1997 17% of the theoretical yield of IGIV from U.S. plasma was shipped to European markets.

Price Issues

ZLB supplies all IGIV to our worldwide distributor Novartis Pharma Ltd. at an ex-factory price which is established in our Marketing and Distribution Agreement. Basically, there is one single ex-factory price for all IGIV supplies worldwide. However, the ex-factory price for the United States is slightly below. This price was not changed during the last 15 months. Since we have no control over the marketing and distribution, we cannot comment further.

Status of Efforts to Increase Production

The present capacity of ZLB to manufacture IGIV is fully exploited today (> 95% of capacity). In critical/ bottleneck areas, manufacturing operations run 7 days a week during 24 hours.

Since the yield of IGIV is - compared with our competitors - already at a very high level further improvement of this yield will be difficult to achieve.

Despite these facts, ZLB already made (see results of first quarter 1998) and will continue to make every effort to contribute to the elimination of the IGIV shortage in the United States.

- ZLB is prepared to ship all IGIV manufactured from U.S. plasma back to the U.S. market.

- Based on the increased delivery of IGIV in the first quarter 1998, we are confident to ship 1998 25% more products to our distributor in the United States. Under consideration of our past experience (1996-1997) additional 13% of IGIV manufactured will get lost due to withdrawals with respect to CJD and preventive measures to keep these withdrawal risks at a minimum. Implementation of pool size limitation will further reduce the IGIV output at ZLB.

- ZLB already started a significant investment in the expansion of the manufacturing capacity for albumin and IGIV. However, the benefit of this investment will depend on the time to approval for this new equipment and the shut-down period necessary to make some important adaptations in our infrastructure.

Ruedi Weg-

Mr. SHAYS. Thank you, Dr. Wager. I'm just going to ask you a few questions, then we're going to let you go on your way. Basically, we have the Red Cross before us. Correct? This is both Swiss and American. So, I make an assumption that you are all partners in this process. Is that a fair assumption?

Mr. YETTER. Let me speak to that, Chairman Shays. I represent Novartis Pharmaceuticals Corp. here in the United States which is a U.S. company. Our affiliate, Novartis Pharma AG in Switzerland is the party that has the agreement with the Swiss Red Cross.

Mr. SHAYS. But you're the distributor——

Mr. YETTER. And we are the distributor here in the United States.

Mr. SHAYS. So, we'll be able to cover that. And Dr. Wager, I'll just ask you a few questions. Did your company see demand rise since you said, you are looking to have your production go up 50 percent this year, if it's licensed, in other words, approved. You've already begun setting up the facility. You're waiting to be approved. Is that correct?

Mr. WAGER. That is correct. We decided on the expansion of our manufacturing facility in 1995, and started effectively in some areas in 1996.

Mr. SHAYS. And you sell where throughout the world?

Mr. WAGER. We are selling from Japan through the United States. The majority of our sales are in Europe and in the United States.

Mr. SHAYS. And did I misunderstand you, do you say you're the biggest fractionator?

Mr. WAGER. We are in the voluntary non-remunerated donor area by far. In other words, in the recovered plasma field, we are the biggest fractionator.

Mr. SHAYS. OK. Of volunteer donors?

Mr. WAGER. Yes.

Mr. SHAYS. And what basically we have before the committee now are volunteer donors as opposed to purchased donors?

Mr. WAGER. That's correct.

Mr. SHAYS. OK. Maybe you could describe to me what you think the significant difference between volunteer versus paid is?

Mr. WAGER. It's, there are a couple of aspects of first moneys, of course. The volunteer non-remunerated donors are giving their blood only for patients, needing blood products. And they are not paid at all, contrary to the source plasma which is manufactured by the blood product industry where the donors are paid.

Mr. SHAYS. So what do I make of the significance. You want it to be very clear to us that all donated blood comes back to the United States, and I think that's one of your points. Correct?

Mr. WAGER. That's correct.

Mr. SHAYS. Yes, and I make an assumption that given it was donated blood, you'd feel that maybe there's more of a need to make sure we know that it's returned to the United States?

Mr. WAGER. I didn't understand——

Mr. SHAYS. I'm sorry. What I'm sensing from you is that you want me and the committee, the staff and so on, to clearly understand that if you voluntarily give blood to the Red Cross and oth-

ers, that it is going to come right back to the United States, even though it is produced in Switzerland. Is that your point?

Mr. WAGER. Yes, that is an agreement we made with our distributor, at least, for the period where there's really a shortage of IGIV in the United States.

Mr. SHAYS. Well, I think that's important to make, and I appreciate you for making the point. We'll make sure that it's understood. Does any of your production facility that relates to the United States have to be approved by the FDA in the United States?

Mr. WAGER. That's correct. All our manufacturing operations and installations in Switzerland are approved by the FDA, and are regularly inspected by the FDA. And we have to apply for a new establishment license as well, if we expand for that facility.

Mr. SHAYS. Is the blood donated? The plasma that you return and its by-products to Japan, is it basically donated from Japan, more or less, or are there correlations too.

Mr. WAGER. No, we have today only two sources for our plasma, United States and Europe, which is roughly 50–50.

Mr. SHAYS. OK. Before you get on your way, is there anything else that you want us to know. You were here for some of the hearing. Is there any comment that you want to just make sure, other than your statement that is on the record?

Mr. WAGER. No, the only thing I would like to underline which was discussed today if we can, as one of the measures, speed-up the licensing of new equipment installations and adaptations by the FDA. That would be a great contribution to resolve part of the shortage.

Mr. SHAYS. Now, let me ask you this because this is a recommendation of the preceding panel. I make an assumption, but tell me if I'm wrong? I make an assumption that the equipment clearly, is very complex, and there are lots of procedures that have to be followed to guarantee a near-perfect blood supply. But, I also make the assumption that this equipment has been seen in the past by FDA. You are expanding what you already do. So that they don't have to re-evaluate the equipment. They just have to make sure it performs as it was manufactured to perform?

Mr. WAGER. No, that is not correct.

Mr. SHAYS. OK.

Mr. WAGER. Each new equipment you are bringing in the manufacturing operation has to be validated or re-validated, and fully documented. And if there is a major change, for instance, a new machine you're buying, validating, then you have to submit it to the FDA, and you have to wait for approval. The FDA goes through all the documentation, and that process takes at least, several months.

Mr. SHAYS. OK, but what I want to understand, remember you're talking to someone who will need to visit a facility, and see it firsthand, and I commit to doing that—at least to one—what I want to be clear on is that if the machine is similar to a machine already approved, and this machine hasn't been validated, I make an assumption that validating is not that complex a process. It's more paperwork. Is that a false assumption?

Mr. WAGER. No, that is correct. The difference is not very big regarding the validation work and the documentation.

Mr. SHAYS. If you bring in changes to that machinery, then, I make an assumption that you then have to go through a more complex approval process or validation process.

Mr. WAGER. No, basically not. Each new machine has to be validated and anyway, has to be approved by the FDA.

Mr. SHAYS. And does validation also mean actually having the machinery run, and——

Mr. WAGER. Exactly.

Mr. SHAYS. OK. That's something we'll bring up with FDA, and we'll see what's involved. I'm sure part of it is personnel.

Mr. WAGER. And the second recommendation I would like to make to the subcommittee, that again, the policy regarding the withdrawals due to Creutzfeldt Jakob is re-evaluated in 2 days in light of figures and facts.

Mr. SHAYS. I want to be clear on this. I didn't hear quite what you said. What are you saying, you had to destroy 7 percent of your supply? Now, are you saying you want to be able to sell it knowing that there is the potential for this infectious agent? I'm not hearing quite what you're saying?

Mr. WAGER. According to the 2-day rule of the FDA, you have destroyed this material, and this material is not any longer available for patients. I think there is first, coming inside a better understanding and comprehension of Creutzfeldt Jacob today. And I think we should continuously re-evaluate whether these policies are still correct or not.

Mr. SHAYS. OK, I'm sorry. I'm missing something in the accent, too. Maybe it's just been a long day. Since you want to make this point, and, I think it's come up before, Creutzfeldt-Jakob Disease, when we determine that a unit of the processing has been contaminated, we are requiring that that plasma cannot be used. Are you saying you agree with that decision or disagree with decision?

Mr. WAGER. I would like to make first, a complimentary remark to your question. We are deciding today to destroy blood products if the blood donor suffered from Creutzfeldt Jakob. Second, there is no proof that Creutzfeldt Jacob has ever been transmitted by a blood product. And I think we should carefully balance the IVIG or the IGIV shortage on the one side, and the destruction of material which has an unmeasurably low risk of a transmission of any disease.

Mr. SHAYS. So, your answer would be, yes. You believe you should be able to sell that product, given that you don't think there is a risk. I guess my question is, under those conditions, would you advocate that it be noted that these vials basically, have been determined to have Creutzfeldt-Jakob Disease, but that the risk is minimal?

Mr. WAGER. That is my very personal point-of-view.

Mr. SHAYS. OK.

Mr. WAGER. The risk is unmeasurably low, and I would do it. On the other hand, as a company CEO, I have to take care of liability issues as well. So there is a balancing "between."

Mr. SHAYS. So, what I'm hearing you say is that, as a CEO, there's a liability question; that's one issue. But, you're saying be-

cause of the shortage, and given that the risk is minimal in your judgment, and probably in the judgment of most people, that you should be allowed to sell this product. Yet you would agree that you would note that it has been separated. You have separated that plasma group?

Mr. WAGER. That is correct.

Mr. SHAYS. OK. Anything else you want to say?

Mr. WAGER. No, that is all. Thanks for asking.

Mr. SHAYS. I hope you make your plane, and have a safe flight home. We appreciate you being here. Sorry it took so long to get you to the panel here.

Mr. WAGER. Thank you, very much.

Mr. SHAYS. Thank you, very much. We will continue. I appreciate all the witnesses allowing that dialog, and we'll just go down the line and do your statements. And I want to say to you, I want you to say your statements as you want to say them. If you want to abbreviate them, that's fine. I don't have a time restraint, and my view is, if you waited to the fourth panel, I'm going to wait as long as you want to wait. Thank you.

Mr. MCDONOUGH. Thank you, Chairman Shays.

I am Brian McDonough, chief operating officer and responsible head for the American Red Cross Blood Services, and I thank you for this opportunity to respond to your concerns about the current shortage of IVIG in the United States.

As a non-profit humanitarian organization, the American Red Cross is especially sensitive to these concerns. As you will hear, the continuity of care for the many patients who depend upon immune globulins is of great importance to us as well. And we are committed to doing all that we can to increase the amount of product available to meet the needs of these patients.

The principle role of the Red Cross Blood Services is that of the Nation's largest supplier of transfusable blood components, serving more than 3,000 hospitals across the country. The American Red Cross collects almost 6 million units of blood from 4.5 million voluntary donors.

For the purposes of today's discussion, however, it is important to distinguish the role of us as a provider of these transfusable blood products from that which we play in the provider role of plasma derivatives. Consistent with the needs of transfusion medicine, units of whole blood are separated into their specific components following donation. These are red cells, platelets and plasma. Approximately 80 percent of the plasma Red Cross recovers from these 6 million volunteer donations is then fractionated into these plasma derivatives, and these derivatives account for 15 to 20 percent of our Nation's supply.

With respect to IGIV, approximately 10 to 15 percent, or 3 million grams used by patients is derived from the Red Cross recovered plasma. Overall, the shortage of IVIG has been caused by a number of factors, as you heard today, including increased demand by physicians and patients, and issues with respect to production and product withdrawals. As a review of available market research indicates, the demand for IGIV in the States has risen steadily since the 1980's, climbing from 40,000 grams in 1981 to a level of nearly 18 million grams this year.

The subcommittee has raised concerns that manufacturers and distributors of IGIV may be stockpiling the product. We'd like to affirm that this is certainly not the case with the American Red Cross. The average number of days from the time the Red Cross receives finished immune globulin product from our contract manufacturers, until it is distributed to hospitals is less than 14 days. And as of late April, more than 40 percent of our annual volume was on back-order.

The dramatic increase in the demand for IGIV has coincided with unprecedented problems of supply. And from the standpoint of the American Red Cross, and in sharp contrast to the testimony that you've heard from others today, withdrawals associated with CJD have had a particularly severe impact on our ability to provide these derivatives. Whenever a volunteer donor or donor's family provides medical information related risk factors for CJD, the Red Cross takes action consistent with FDA policy. If medical information warrants, the Red Cross permanently defers any donor and voluntarily withdraws all transfusable blood components and plasma derivatives manufactured from his or her previous donation. If plasma recovered from these donations is in process at our contract manufacturing facilities, it is immediately placed into quarantine, and subsequently destroyed.

In our written testimony, we've provided two examples where the Red Cross received medical information from donors following a donation, and was faced with trying to get medical records many, many years after the fact. Frequently, these medical records are simply not available. However, in most all instances, where we can access medical records, we find that the donor is truly not at risk for CJD. The result, however, is a substantial delay in the delivery of these products to patients or the destruction of product even when there is no confirmation that the donor really is at-risk for CJD.

In one of the examples we provided to the subcommittee in our written testimony, 1,071 patient doses of IGIV were placed in quarantine, and not able to be released for almost 6 weeks until we could confirm that the donor had not received human growth-derived pituitary growth hormone. As such, the current FDA criteria for withdrawal and quarantine of CJD-implicated products has directly impacted the supply of Red Cross material.

Mr. Chairman, as we shared with you in a meeting almost a year ago, the impact of CJD-related withdrawals upon product availability for the Red Cross is of great concern. From July 1997 through the end of March 1998, the American Red Cross has lost one-quarter of its supply of IGIV due to CJD-related issues. The Red Cross wants to take responsible actions consistent with the best available science, and we endorse the HHS Advisory Committee on Blood Safety and Availability's recommendation that the FDA reconsider its withdrawal guidelines to the extent appropriate to relieve product shortages and protect safety.

From the Red Cross point of view, part of the solution to the supply will be to increase the volume of plasma that the Red Cross has available for fractionation into these derivative products. In 1999, we will increase the available volume by increasing our blood donations, and by entering into agreements with other volunteer blood

collectors. In the meantime, we will continue, as we have done since late 1997, to respond to emergency requests for IGIV outside of our existing contractual arrangements, a number approximating 10 to 15 such requests per day.

By the end of 1999, through our efforts with our contract manufacturers, the Swiss and Baxter, and through increased collections, the Red Cross hopes to almost double the amount of IGIV we provide to patients from our volunteer plasma to almost one-third of the present U.S. demand.

To address the larger issue of transmissibility of CJD through transfusable components and plasma derivatives, the Red Cross has committed today over $1 million to research studying possible links between CJD and transfusion, more we believe, than any other private organization. We have several research studies underway at our Holland Laboratory, and in collaboration with Dr. Paul Brown at the National Institutes of Health, and Dr. Bob Rohwer at the Veterans Administration.

In conclusion, the Red Cross remains committed to meeting the needs of America's patients, hospitals and physicians, by improving the safety and availability of plasma derivatives derived from volunteer donors of whole blood. It is incumbent upon us, as stewards of this precious national resource, to optimize its availability for patient use.

I would like to thank you, Mr. Chairman, Representative Towns, and members of the subcommittee for this opportunity to be a part of the hearing to explore these critical issues. And more importantly, or equally important for providing us with an opportunity to share with the patient groups assembled here today, an overview of the Red Cross's actions to increase the safety and availability of this important plasma product. Thank you.

[The prepared statement of Mr. McDonough follows:]

Chairman Shays, Representative Towns, and Members of the House Human Resources Subcommittee, I am Brian McDonough, Chief Operating Officer and Responsible Head of the American Red Cross Blood Services (ARCBS). Thank you for this opportunity to respond to Congressional concerns about the current shortage of intravenous immune globulin products in the United States. As a not-for-profit humanitarian organization, the American Red Cross is especially sensitive to these concerns. As you will hear, continuity of care for the many patients who depend upon immune globulins is of great importance to the American Red Cross. We are committed to doing all we can to increase the amount of product available to meet the needs of patients in the United States.

The principal role of American Red Cross Blood Services is that of the nation's largest supplier of transfusable blood components, serving more than 3,000 hospitals across the country. The American Red Cross collects almost 6 million units of whole blood through the generous donations of 4.5 million volunteer donors annually. This year, during which the American Red Cross celebrates 50 years of leadership in meeting the nation's need for blood services, also marks the completion of a seven-year, $287 million program to transform the way the Red Cross collects, tests, and distributes almost one-half of America's blood supply. Under the leadership of Mrs. Elizabeth Dole, President of the American Red Cross, a state-of-the-art system has been created which will meet the blood banking challenges of the next century. Indeed, at a ceremony kicking off the 50-year celebration just last week, Dr. David Kessler, Dean of Yale University School of Medicine and former Commissioner of the FDA, characterized Mrs. Dole's actions as "nothing short of an heroic effort....to transform the safety of this country's blood supply."

Role of ARC in provision of Immune Globulin Products

For the purposes of our discussion today, it is important to distinguish the role of the Red Cross as a provider of transfusable blood components, from that which it plays in the provision of plasma derivatives. Consistent with the needs of transfusion medicine, units of whole blood are separated into specific components following donation -- red blood cells, platelets and plasma. Because of the relatively limited need for plasma for transfusion, most of the plasma recovered from whole blood donations is processed, or fractionated, into various plasma derivatives. Approximately 80 percent of the plasma Red Cross recovers from six million volunteer blood donations of whole blood is fractionated into plasma derivatives. Red Cross plasma derivatives account for 15 to 20 percent of the nation's supply. Plasma derivatives manufactured for Red Cross include Factor VIII concentrate used by persons with hemophilia, albumin used to restore plasma volume in treatment of shock and burns, and intravenous immune globulins, or IGIV, used to treat immune disorders. With respect to IGIV, approximately ten to 15 percent, or 3 million grams, of the IGIV used by patients in the United States is derived from Red Cross recovered plasma. Consistent with its mission, the Red Cross is traditionally a low-cost provider of IGIV.

Unlike the commercial providers of plasma derivatives, the Red Cross does not fractionate its plasma derivative products. We contract with commercial fractionators to manufacture IGIV,

antihemophilic factor and albumin products. These plasma derivative products are returned for distribution under the American Red Cross label to hospitals, and other intermediaries. Approximately 80 percent of Red Cross recovered plasma is fractionated at Baxter Healthcare's Hyland Division under that company's FDA license. Polygam SD, the IGIV product manufactured for us by Baxter, is distributed to hospitals and patients within the United States, 70 percent under contract with the University Health System Consortium and Premier Purchasing Partners. The remainder is distributed directly to domestic hospitals, home care companies, and wholesalers. In response to any product shortage, the Red Cross gives priority to its contractual commitments and to filling emergency orders.

The remaining 20 percent of American Red Cross recovered plasma is sent to the Swiss Red Cross, licensed by FDA to manufacture this plasma into albumin and IGIV.[1] Historically, IGIV produced by the Swiss Red Cross, was distributed by Novartis, a pharmaceutical company based in Europe. Approximately, 70 to 90 percent of this IGIV, sold under the name "Sandoglobulin" was distributed to patients in the United States. In sum, therefore, approximately 96 percent of the IGIV manufactured from American Red Cross recovered plasma, including IGIV that the American Red Cross distributes, is used today to treat patients here in the United States.

In 1997, the Swiss Red Cross renegotiated its agreement with Novartis, and subsequently entered into a collaboration with the American Red Cross. As a result of these new agreements and pending FDA approval, the American Red Cross, starting in June 1998, will distribute IGIV product manufactured by the Swiss Red Cross from our recovered plasma, under the trade name Panglobulin. We entered into this arrangement because one of the Red Cross' key policies is that any plasma products manufactured from our plasma should be returned to the Red Cross to first address the needs of patients in the United States.

Reasons for Shortage of ARC Product

I would now like to address the causes for the short supply of Red Cross immune globulin products. As the members of this Subcommittee have heard, commercial fractionators and distributors have experienced shortages in intravenous immune globulin and albumin during the past year. Overall, the shortage of immune globulin has been caused by a number of factors, including increased demand by physicians and patients; issues with respect to production; and product withdrawals. A review of available market research indicates that the demand for IGIV in the United States has risen steadily since the early 1980's. Demand grew at a rate of more than 1 million grams per year during the early 1990's, climbing from 40,000 grams in 1981 to a level of 18 million grams this year.

The Subcommittee has raised concerns that manufacturers and distributors of IGIV may be stockpiling product. This is certainly not the case with the American Red Cross. The average

[1] The logistics of blood collection and component processing are such that approximately 20 percent of the plasma that Red Cross recovers, generally from donations in rural areas, cannot be processed into components and frozen within 24 hours. Baxter is licensed to fractionate IGIV from plasma frozen within 24 hours of collection.

number of days from the time the Red Cross receives finished immune globulin product from our contract manufacturers, until it is distributed to hospitals and patients is less than 14 days. As of late April, 126,426 grams of IGIV were on back order -- that's more than 40 percent of the total number of grams distributed by the Red Cross in a year. We prioritize our response to back orders based on emergency or guaranteed contract commitments.

The dramatic increase in demand for the IGIV has coincided with unprecedented problems of supply. From the standpoint of the American Red Cross, withdrawals associated with Creutzfeldt-Jakob Disease, more commonly referred to as CJD, have had a particularly severe impact on our ability to provide vitally needed plasma derivatives. The impact of CJD is based upon a theoretical, unproven risk. In fact, according to CDC, there has never been a reported case of CJD transmission by a plasma derivative, or transfusable blood component. However, the Red Cross takes action whenever a volunteer blood donor, or a donor's family, provides medical information related to risk factors for CJD. If medical information warrants, the Red Cross permanently defers any donor and voluntarily withdraws all transfusable blood components and plasma derivatives manufactured from his or her previous donations. If plasma recovered from these donations is in process at our contract manufacturing facilities at the time post donation information is received, it is immediately placed into quarantine and subsequently destroyed.

The vast majority of our CJD-related withdrawals are associated with healthy donors who report that they may have received human growth hormone as a child, or pooled dura mater transplants in the course of brain surgery. A recent example involved a young woman, who after donating for the first time, spoke with her parents and discovered that she had received some type of growth hormone when she was a child. The Red Cross initiated a lengthy investigation, which involved contacting the three physicians, at two different institutions, who had treated her years earlier. Finally, after six weeks, we confirmed that the donor had received recombinant, not human, growth hormone, and as such was not considered to be at risk for CJD. During this six week period, however, approximately 150,000 grams, or 1,071 patient doses, were withheld from hospitals and other suppliers.

A second example involves a donor who reported receiving a dura mater transplant over 30 years ago, from a well-established institution, but could not say whether it was pooled dura mater. Under FDA guidance, derivatives from donors who have received a dura mater transplant can only be released for patient use if the dura mater was not pooled during processing; was processed in the United States; and if an autopsy of the dura mater donor demonstrates that the donor is free of neurological disease. Therefore, after the blood donor informed us of his surgery, a Red Cross physician spoke with the head of the treating institution's neurology department, who stated with certainty that the dura mater used in the transplant would have been obtained from a U.S. source which did not pool dura mater. However, without medical records to indicate that an autopsy had been done on the donor of the dura mater, which could subsequently rule out evidence of neurological disease, the Red Cross had to quarantine all products associated with the original blood donor and place him on the permanent donor deferral registry. This withdrawal resulted in the quarantine of 50,000 grams of IGIV, the equivalent of 357 patient doses, from the market.

In both cases, the Red Cross was faced with trying to get medical records many, many years after the fact. Frequently, these medical records are not available. However, in almost all instances where we can access medical records, we find that the information given by the donor is incorrect or incomplete, and in fact, that the donor is not at risk for CJD. The result however, is either a substantial delay in the delivery of products to patients, or destruction of products even when there is no confirmation that the donor is at increased risk of CJD. As such, the current FDA criteria for withdrawal and quarantine of CJD-implicated products has directly impacted the supply of Red Cross IGIV product.

Mr. Chairman, as we shared with you in a meeting almost a year ago, the impact of CJD-related withdrawals upon product availability is of great concern. **From July 1997 through the end of March 1998, the American Red Cross lost almost one quarter of its supply of IGIV due to CJD-related withdrawals:** ten percent of the Red Cross supply of immune globulin was withdrawn and destroyed; another six percent was either placed in quarantine, or was returned by hospitals or patients; and six percent of the starting material, commonly referred to as intermediates, was lost due to CJD-related withdrawals because they could not be processed into final container material. In total, product withdrawals related to CJD have resulted in $130,000,000 worth of lost product since late 1994.

The Red Cross wants to take responsible actions consistent with the best available science. We endorse the HHS Advisory Committee on Blood Safety and Availability recommendation that FDA reconsider its CJD withdrawal guidelines to the extent necessary to relieve product shortages.

As members of the Subcommittee are aware from the hearing in July 1997, efforts to reduce the size of plasma pools for manufacture of Red Cross plasma derivatives are underway. The Red Cross has worked with its contract manufacturers to reduce the number of donations included in pools used in the manufacture of our plasma derivatives by limiting the number of recovered plasma donations to no more than 60,000 per pool. It is important for the purposes of today's discussion to note that efforts to consistently reduce pool size have resulted in a less efficient manufacturing process, and led to a four percent loss of IGIV product during the same time period, between July 1997 and March 1998. Although the relationship of pool size to the safety and efficacy of IGIV has not been clearly established, we remain committed to reducing pool sizes associated with the manufacture of plasma derivatives.

Mr. Chairman, in response to the request of your staff, I wish to briefly comment on the Red Cross' new fresh frozen plasma product, Solvent-Detergent Fresh Frozen Plasma. The opportunity to provide millions of patients with a transfusable component that cannot transmit HIV, HBV, HCV or any other lipid envelope virus and which will also result in fewer instances of bacterial contamination is very exciting. But the Red Cross is committed to ensuring that the advances represented by this product not come at the expense of those who need plasma derivatives. The launch of solvent detergent treated fresh frozen plasma has not contributed to the shortage of IGIV. Moreover, to the extent that some FFP will be lost in the viral inactivation process, our increased collections and agreements with other blood collectors to obtain additional recovered plasma will

more than make up for the loss.

What the Red Cross Is Doing to Increase Availability of Product:

For the Red Cross, part of the solution to the supply problem will be to increase the volume of plasma that the Red Cross has available for fractionation into plasma derivative products, including IGIV. This has been relatively consistent since 1996, but in 1999, we will increase the available volume by increasing donations, and by entering into agreements with other volunteer blood collectors. In the meantime, we will continue, as we have done since late 1997, to respond to emergency requests for IGIV outside of our existing contractual arrangements with hospitals and intermediate distributors. At present, we are able to fill ten to 15 such requests each day.

Work with Contract Manufacturers to increase availability of IGIV:

It should be noted that the American Red Cross has chosen to work with more than one fractionator, in an effort to minimize potential disruption in supply that might result from a problem with any one manufacturer.

Assuming FDA approval of Panglobulin, the American Red Cross anticipates that beginning in June two-thirds of the IGIV manufactured by the Swiss Red Cross from ARC-recovered plasma will be available for distribution as a Red Cross product. The overwhelming majority of product not sent back to ARC will be distributed under the Novartis label in the United States. In 1999, ARC will receive 80 percent of the IGIV processed by the Swiss, ramping up to 100 percent in 2000.

In addition, the Red Cross and Baxter are working to optimize the output of Polygam SD. Pending FDA approval of a product license supplement to allow the use of a new resin in the purification process, Baxter/Hyland plans to increase the output of IGIV from Red Cross plasma from a rate of 2.4 million grams per year to almost 3 million grams by early 1999. Thus, by the end of 1999, through our efforts with our contract manufacturers (the Swiss Red Cross and Baxter) and increased collections, the American Red Cross hopes to almost double the amount of IGIV it provides to patients from our volunteer plasma to meet almost one-third of the present US demand.

Efforts to Address CJD:

To address the issue of post-donation information, a new pre-donation screening step was recently introduced by the American Red Cross to further alert potential donors to conditions which could lead to a product withdrawal due to CJD. This pre-screening is a one-page notice, separate from the blood donation questionnaire, but with questions repeated from the questionnaire. The notice instructs individuals not to donate if they, or any blood relatives, are at risk for CJD; have ever had a dura mater transplant; or have received human pituitary-derived growth hormone.

We have also taken steps to reduce the likelihood that plasma from a donor subsequently diagnosed with CJD is included in pools for fractionation. CJD is a disease of older people, with a mean age

of incidence of 67. The Red Cross only uses plasma from donors 59 years old or younger for fractionation, thus eliminating the age group at greatest risk from plasma pools.

To address the larger issue of the transmissibility of CJD though transfusable components and plasma derivatives, the American Red Cross has committed over $1 million to research studying possible links between CJD and transfusion, more than any other private organization. The Red Cross takes all potential threats to blood and plasma safety very seriously, and we have moved aggressively to expand the body of scientific information related to CJD. We have several research studies underway at our Holland Laboratory and in collaboration with Dr. Paul Brown at the National Institutes of Health and Dr. Robert Rohwer at the Veterans Administration. In response to a request by the FDA, we have redesigned one of our experiments to demonstrate in animal models whether there is transmissibility in certain plasma fractions. At FDA's request, this experiment will be repeated at an independent laboratory. The Red Cross is also continuing to work with Marian Sullivan, of the AABB, who is directing a CJD "lookback" study, involving 179 recipients of blood transfusions from donors subsequently diagnosed with CJD. These recipients have been followed for up to 25 years following transfusion. None of the recipients has died of CJD or shown any sign of the illness.

Conclusion

The American Red Cross remains committed to meeting the needs of America's patients, hospitals and physicians, by improving the safety and availability of plasma derivatives derived from volunteer donations of whole blood. It is incumbent upon us, as stewards of this precious national resource, to optimize its availability for patient use. I would like to thank you Mr. Chairman, Representative Towns, and Members of the Subcommittee for the opportunity to be part of this hearing to explore the critical issues surrounding the current shortage of immune globulin in this country. And most importantly, for providing us with an opportunity to share with the patient groups assembled here today, an overview of the Red Cross' actions to increase the safety and availability of this important plasma derivative.

Mr. SHAYS. Thank you, Mr. McDonough. This is going to be an interesting issue for us to talk about. It's a little different than what we've talked about so far. So, I'll look forward to that dialog.

Mr. Yetta.

Mr. YETTER. Yes, Chairman Shays and Congressman Towns, it's my pleasure to be here today.

I'm Wayne Yetter, president and chief executive officer of Novartis Pharmaceuticals Corp. Novartis Pharmaceuticals Corp. is a major U.S. pharmaceutical company affiliated with a leading global group of companies providing healthcare, nutrition, and agricultural products and services. Novartis Corp. employees over 20,000 people here in the United States. While Novartis Pharmaceuticals Corp., a subsidiary of the Novartis Corp. employs over 7,000 people in the United States, and Novartis markets one brand of IVIG sandoglobulin, which is the only blood product that we sell and distribute.

We commend your efforts to try to get to the bottom of this shortage and hope to avoid any future crises. Thank you for the invitation to appear before you today, and Novartis Pharmaceuticals Corp. is committed to doing all that it can to address the nationwide IVIG shortage in the interest of patients who depend on this important drug.

As my colleague, Dr. Dunsire will explain shortly, Novartis has taken critical steps to address this shortage. We've made the manufacturer of the product, as you heard, the Swiss Red Cross, acutely aware of the crises and the shortage here in the United States, and have asked for more product, and they're responding to the best of their capability.

We've attempted to speed delivery of the product through the practice of drop-shipping the product to end-users, instead of shipping to wholesalers, and are taking steps to make sure that the product gets to the end-user and to the patients that need it. And it also avoids the development of any secondary markets.

We have also established an emergency hot-line. This was established as early as last December to make available limited supply of product to critical-ill patients whose doctors certify an urgent need. And we continue to work with our customers to help better manage the supplies that are available to us.

I'm joined today by Dr. Deborah Dunsire. Dr. Dunsire is a physician and is vice president of our oncology business unit. This is the unit that has responsibility for our IGIV product, and as I mentioned, is the only blood product that we sell. She really is the most knowledgeable person within Novartis about the current shortage, and the specific steps that we have taken to meet this critical crisis, and to meet the needs of our customers and patients.

At this time, I'd like to ask Dr. Dunsire to address these important issues.

Dr. DUNSIRE. Congressman Shays, Congressman Towns——

Mr. SHAYS. Happy to have you make a statement. Thank you.

Dr. DUNSIRE. I beg your pardon?

Mr. SHAYS. I'm happy to have you make a statement. Thank you.

Dr. DUNSIRE. I'm happy to be here. We're happy to have the opportunity to work with the subcommittee assessing this severe

shortage of immune globulin, and to explain what we've been doing to address it.

Our product, Sandoglobulin, you have heard is manufactured at the ZLB facilities in Bern, Switzerland. To the best of our knowledge, all U.S. eligible product, in other words, product manufactured from U.S. derived plasma, and U.S. licensed facilities, is being shipped back to the United States of America. The amount of Sandoglobulin available to us for U.S. patients has increased each year since 1996. While in 1998, the forecast was consistent with our expected demand, it was made prior to the shortage. The shortage became apparent as we all heard in late 1997, and we noticed that through enormous increase in phone calls to Novartis requesting product.

From our perspective, the shortage is complex, and results from the interaction of many different factors, most of which are beyond Novartis' control. First and foremost in our minds, the shortage stems from reduction in supply from the four U.S. manufacturers when their plants faced GMP compliance issues causing severe slow-downs in manufacturing. This started in the fall of 1996 as you heard, and we believe, that while the market could adapt to this one supply shock, it was unable to compensate when the other three manufacturers faced similar issues in the fall of 1997. These issues are still affecting supply today. We believe that when compliance issues are fully resolved, the U.S. needs for IVIG are likely to be met with all manufacturers and distributors making product available.

The second factor contributing to the shortage was withdrawal of product due to the theoretical risk of transmission of CJD. We have faced four withdrawals already in 1998. While only 3.6 kilograms of product was returned, approximately enough for 120 adult doses, this represents only the tip-of-the-iceberg. Product that's in production is also lost, and you heard about that from Dr. Wager, and also from the American Red Cross.

The third factor magnifying the shortage is the increase in demand for IGIV physicians have found the product useful, and are using it in a variety of settings. We would agree that the demand is increasing around 10 percent a year.

We're taking the shortage extremely seriously, and despite it, we try and serve as many of our customers as we can reasonably accommodate. While the causes of the shortage are beyond our control we have implemented the following measures to try and manage through this shortage: We have requested that more product be made available, and reflected our willingness to accept as much U.S. eligible material as we can get. The ZLB tells us that their capacity has been exceeded and they can't increase production right now.

We established a medical emergency hot-line in December, prior to the FDA's request to companies to do so. Over 3,700 people have received Sandoglobulin through this program to-date. We continue to get close to 1,000 calls per week to this hot-line. We try to efficiently and quickly get the product available to us, to critically ill patients by shipping inventory promptly. We do not sit on product, and indeed, inventories have declined significantly in the last 6 months versus prior levels. Additionally, as you heard, we drop-

ship to end-users, not only to speed the product delivery, but to try and prevent the development of secondary markets.

Unfortunately, we're also not able to support any new clinical trials at this time because of the shortage. And at this moment, our sales force does not promote the product.

As to the specific question as to what can be done to alleviate the shortage, we believe that once the U.S. manufacturers are back in compliance, and we're all supplying at our prior levels, that we will be able to meet demand in the marketplace. In the interim, we believe the most useful measures would be to examine importation of derivatives of plasma from other sources within the world, and you heard that discussed in the last panel. It would involve significant FDA review of off-shore plasma supplies and manufacturers, however.

It's also valuable to re-examine the criteria for CJD withdrawal, and be sure that they appropriately balance risk versus accessibility. We continue to encourage rapid regulatory review of product lots for release, and facility validation. And last, it may be appropriate to continue to encourage restraint in the use of IGIV through the development of expert consensus guidelines.

Novartis Pharmaceuticals Corp. will continue to work diligently with this subcommittee to be part of the solution to this serious problem. I thank the committee for its time.

[The prepared statement of Mr. Yetter and Dr. Dunsire follows:]

Summary

The U.S. is experiencing a serious shortage of intravenous immunoglobulin (IGIV) at present. Novartis Pharmaceuticals Corporation, a major U.S. pharmaceutical company, markets and sells one brand of IGIV - Sandoglobulin®. We desire to work with all interested parties to try to achieve a timely resolution to this grave issue.

Sandoglobulin is the only blood product we sell and we do not manufacture it. The product is manufactured from plasma derived from unpaid American donor blood at the Central Laboratory of the Swiss Red Cross (ZLB) facilities in Bern, Switzerland. To the best of our knowledge, all of the "U.S. eligible" Sandoglobulin manufactured by the ZLB is currently returned to the U.S.

The amount of Sandoglobulin available to us for U.S. patients has increased year on year since 1996. This 1998 forecast was consistent with forecasted demand. Our demand forecast, however, was made prior to the shortage, which has been experienced since November of 1997, predominantly due to the reduction in supply from major U.S. manufacturers.

From our perspective, the shortage is driven by the complex interaction of many factors beyond Novartis' control:

Reduction in Supply

First and foremost, the shortage stems from unexpected reductions in supply from the four U.S. manufacturers when their plants faced GMP compliance issues causing severe slowdown in manufacturing. This started in the fall of 1996 with one manufacturer. While the market was able to adapt to this reduction in supply, it could not further compensate when the other three manufacturers faced similar issues in the fall of 1997. These issues are still affecting the supply of IGIV today. When these compliance issues are fully resolved, the U.S. needs for IGIV are likely to be able to be met with all manufacturers and distributors making product available.

Withdrawals for CJD Risk

The second factor contributing to the shortage is the withdrawal of product for the theoretical risk of transmission of CJD. We have faced four withdrawals already in 1998 through April of this year. While only 3.6kg of finished product was returned (enough for approximately 120 adult doses) this represents only the tip of the iceberg. Product that is in production is also lost. We are told by the ZLB this represents approximately 15% of the available plasma, intermediates and finished product prior to shipment is also lost due to CJD withdrawals further impacting potential supply to the U.S.

Increased Demand

The third factor magnifying the shortage is the increased demand for IGIV. Physicians have found this product useful in a variety of settings and this over time has led to an increase in market demand in the order of 8-10% per year.

Novartis takes this shortage extremely seriously, and, while the causes of the shortage are beyond our control, we have implemented the following measures to address it.

1. We have requested more product be made available. We have indicated our willingness to accept as much U.S. eligible material we can get. Currently, all U.S. eligible material (i.e., product from U.S. plasma in FDA licensed facilities) which is made available to our company is being shipped back to the U.S. The ZLB has indicated to us that their plant for the manufacture of U.S. eligible IGIV is operating at capacity right now.
2. A "medical emergency hotline" was set up in December, prior to FDA's request to companies to do this. Over 3100 people have received Sandoglobulin through this program to date. We continue to get over 1000 calls per week to the hotline.

4. We drop-ship to end-users to speed product delivery and to help prevent the development of secondary markets through wholesalers.
5. We are not supporting any new clinical trials and our sales force does not promote the product.

What Can Be Done to Alleviate the Shortage

We believe that, once the U.S. manufacturers are back in full compliance with FDA regulations and able to produce at prior levels, the shortfall in the U.S. market can be fully overcome.

In the interim it may be useful to examine:

1. Importing derivatives from plasma from non-U.S. donors manufactured in the rest of the world. This would involve extensive FDA review of offshore plasma suppliers and manufacturers.
2. Re-examining the criteria for CJD withdrawal to ensure that appropriate balance of risk versus accessibility.
3. Continuing to encourage rapid regulatory review of product lots for release and facility validation.
4. Continuing to encourage restraint in the use of IGIV through the development of expert consensus guidelines

Novartis Pharmaceuticals Corporation will work diligently with this Subcommittee to be part of the solution to this serious problem.

Novartis Pharmaceuticals Corporation

Novartis Corporation is an U. S. company affiliated with a leading global group of companies providing healthcare, nutrition and agriculture products and services. It was formed from the merger of Sandoz and Ciba-Geigy in January of 1997 and is headquartered in Summit, N.J. Together with its affiliates Novartis Corporation employs over 20,000 people in the U.S.

Novartis Pharmaceuticals Corporation ("Novartis"), incorporated in Delaware, is the pharmaceutical subsidiary of Novartis Corporation. This company employs over 7000 people throughout the U.S., is headquartered in East Hanover, New Jersey and has facilities in East Hanover and Summit (NJ), Suffern (NY), Maryland, California, Massachusetts, North Carolina, Georgia, Ohio, Illinois, Texas, Arizona, and Colorado. NPC has over 100 products in multiple diverse therapeutic areas including Cardiovascular, Neurology, Psychiatry, Organ Transplantation, Women's Health, Dermatology, Immunology, and Oncology. Sandoglobulin® (Immunoglobulin Intravenous), our only blood product and the focus of our testimony, is managed in the Oncology Business Unit.

Novartis recognizes the critical shortage of immunoglobulin currently existing in the U.S. and is taking this situation very seriously. Novartis wishes to continue to work with patients, prescribers, regulators and other interested parties to achieve a timely resolution of this grave issue.

Manufacture of Sandoglobulin and Collaboration with the ZLB

Novartis neither collects plasma for nor manufactures immunoglobulin, we only market and sell Sandoglobulin.

An independent non-profit company in Switzerland, the Central Laboratory of the Swiss Red Cross (ZLB) manufactures Sandoglobulin. Novartis does not own the FDA registration (the PLA and ELA) for Sandoglobulin in the United States; instead, the ZLB does, and they deal directly with the FDA on issues concerning plant inspection, validation, good manufacturing practices and so on.

The ZLB and our affiliate in Switzerland, Novartis Pharma AG, have had an agreement since 1979 which gives Novartis the right to market the product in a number of countries. Insofar as the U.S. is concerned, our Swiss affiliate has sub-licensed that right to us. Our predecessor company, Sandoz Pharmaceuticals Corporation, began marketing this product in the U.S. in 1984.

The amount of U.S. plasma available to the ZLB from its various sources here is proprietary to them. We are only certain that Novartis Pharma AG, our Swiss affiliate, negotiates with the ZLB a right to a certain amount of what we term "U.S. eligible" Sandoglobulin, i.e., product that is made from U.S. plasma, was manufactured in FDA-validated and complying facilities, and otherwise meets U.S. regulatory requirements. We understand from the ZLB that currently Novartis Pharma AG has access to all their "U.S. eligible" IGIV. As of January 1998,

Novartis Pharma AG is sending us all "U.S. eligible" IGIV available to it from the ZLB.

In prior years, when supply in the U.S. market outstripped demand, small amounts of U.S. eligible IGIV, in the order of 10%, were used to treat needy patients in other countries. The main recipient was the UK. While all eligible IGIV form the ZLB is currently returned to the U.S., this practice has and will continue to put stress on the supply available to needy patients in other countries.

Plasma Source for Sandoglobulin

As a matter of FDA regulation, the Sandoglobulin sold in the U.S. must be sourced from U.S. plasma. The ZLB has independent arrangements with the American Red Cross and other community blood banks here, as well as other organizations abroad, to collect plasma and or pastes for further manufacture into plasma derivatives such as IGIV. The ZLB does not manufacture any intramuscular immunoglobulin (IMIG) anywhere in the world. Novartis does not market and sell any such product.

The plasma from which the ZLB manufactures immunoglobulin comes from collection of whole blood from unpaid donors. This is called "recovered plasma". This distinguishes the product from those sold by the major U.S. manufacturers who use plasma derived by plasmapheresis from paid donors. It is generally believed that unpaid donor plasma is at lower risk for transmission of viral

infections, but it also reduces supplies. This is because paid donors, who donate only plasma instead of whole blood, can donate more plasma more often (maximally 800-900ml two times per week for paid donors versus one unit of blood containing 250 ml of plasma once every 56 days for unpaid donors).

Unpaid donors are generally older than those who are paid for their donations. Since 1994 there have been a substantial number of withdrawals of IVIG and other blood products because of the theoretical risk of transmission of the causative agent for Creutzfeld Jacob Disease (CJD). Blood or plasma considered to be at risk includes that from donors who have been later diagnosed with CJD or those who had received human pituitary derived growth hormone, a dura mater transplant or had two relatives whom were diagnosed with CJD. CJD though rare, occurs more frequently in people over 50 years of age. In addition, pituitary derived growth hormone is less commonly used in recent times with the availability of recombinant growth hormone. Therefore, an older donor pool increases the risk of needing to withdraw plasma from at risk donors. This makes production of derivatives from unpaid donor plasma less attractive because of the loss of product due to CJD withdrawals.

Sandoglobulin

Novartis is proud of the Sandoglobulin safety record. Sandoglobulin, a sterile lyophilized immunoglobulin, has the longest sustained history of

uninterrupted product availability. There has never been an interruption of our supply as a result of manufacturing or other process compliance issues. While there have been CJD withdrawals, Sandoglobulin has never had a documented case of viral transmission. Sandoglobulin is cleared by the FDA for use in the treatment of primary immune deficiencies and immune thrombocytopenic purpura, but it is used for many of the other purposes, including but not limited to bone marrow transplants, pediatric HIV, B-Cell chronic lymphocytic leukemia and Kawasaki Disease.

Shortage

Despite the fact that our supply of Sandoglobulin has not been severely impacted, and should have been sufficient to meet our forecasted demand, there is a severe shortage of immunoglobulin overall in the United States.

It is important to understand that this is not the first time the U.S has had problems in this area, nor is it likely to be the last. Our experience with Sandoglobulin in the U.S. since 1984 has taught that periodic supply shocks are an unfortunate way of life with blood products. We simply are not dealing with a supply of synthetic chemicals for the formulation of a tablet. Instead, we are dealing with an organic supply component, blood, which is vulnerable to infection and otherwise dependent on the vagaries of human donation. The Hepatitis-C withdrawal in 1994 and the CJD withdrawals since 1994 are instructive examples.

In addition, the manufacturing process is complex and slow. Expansion of production capacity is a time consuming and expensive process.

Ultimately, we have a delicate supply coupled with a very complicated and lengthy manufacturing process. Novartis believes that the reasons for the shortage are complex and that there is not a simple solution to the problem. There are three major contributors in our view:

1. Reduction in Supply

We began noticing an enormous increase in phone calls to Novartis requesting product in fall of 1997. While our knowledge of the specifics is not extensive, we believe this was most likely due primarily to the cumulative effect over time of the manufacturing compliance problems experienced by several manufacturers starting in the fall of 1996. We noticed a gradual increase in demand for Sandoglobulin in early 1997, with a dramatic increase by the end of that year as more manufacturers slowed production rates to implement changes to bring them into compliance with FDA regulations. FDA, at the recent HHS Committee on Blood Safety and Availability hearing, put forward an estimate of a 20 % shortfall in the U.S. at this time. This was based on the historical annual 8-10% increase in demand and on market research which showed an approximately 10 % decline in the amount if IGIV sold in the U.S. in 1997. They attributed approximately 80 % of this shortfall

to the compliance issues experienced by U.S. manufacturers. As a result of this and the other factors listed below, eventually all wholesaler inventories were depleted.

2. CJD Withdrawals

In accordance with the FDA's December 1996 "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of CJD by Blood and Blood Products," Novartis has experienced 22 voluntary withdrawals (11/94 –4/15/98) of varying numbers of lots and lot sizes. Approximately 14 kilograms of the finished product Sandoglobulin was returned in 1997 and about 3.6 kilograms in the four withdrawals we have experienced this year (up to April 15).

This small amount of finished goods returned does not adequately reflect the impact of these withdrawals. Most of the Sandoglobulin available to patients is infused within a very short time of its arrival in the U.S. and during this shortage little inventory exists. The major impact is felt in the loss of product in production, which could have come to the U.S. market but for the withdrawal. The ZLB estimates that close to 15% of all of the Sandoglobulin that might otherwise come to the U.S. is destroyed due to these withdrawals. This is because of the necessary destruction of all intermediary pastes and finished product, awaiting final quality checks and shipping, into which the implicated donor's blood was pooled. In order to minimize the impact of these withdrawals, the ZLB has also made changes in its manufacturing process which have negatively impacted yield on production – further reducing potential supply.

While we support all of FDA's efforts to monitor the blood supply, we also support continuous assessment of the December 1996 guidelines in light of the impact it is clearly having on supply.

3. Increasing Demand

Finally, we agree that there has been an increasing demand for immunoglobulin in the U.S. Based on data available to us from "The Marketing Research Bureau" and Arlington Medical Research, two independent audits of the IGIV market, we believe that a figure of 8-10% increase in the overall U.S. market yearly over the past four years is reasonable. Many in the medical community consider the immunoglobulins to be therapeutically interchangeable, and prescribe them for a variety of "on-label" and "off-label" uses, which has always been within the realm of an individual physician's professional medical judgment. There are, in some instances, medical reasons to keep a patient on one form of immunoglobulin once they are stabilized on it.

Novartis' Management of Product During the Crisis

But for the supply shocks discussed above, the amount of Sandoglobulin we are scheduled to receive in 1998 should have been enough to meet our forecasted demand.

1.) We continue to ask both Novartis Pharma AG, our affiliate and, through them, the ZLB, for more product. We have made the ZLB acutely aware of the crisis

here. Our current understanding from the ZLB is that due to plasma supply issues and technical issues relating to plant upgrades, the ZLB cannot increase the U.S. eligible supply for 1998. It is our current understanding that we are getting all U.S. eligible product to which our affiliate is entitled pursuant to its negotiations with the ZLB. This is unfortunately putting some stress on the supplies available to patients in certain other countries.

We do not have information about 1999 or beyond, but again we will ask to receive as much U.S. eligible IGIV as the ZLB can produce.

2.) We have tried to efficiently and quickly get the product that is available to us to critically ill patients. We ship incoming inventory promptly and do not "sit on" product. Indeed, inventories have declined significantly in the last six months.

3.) We are trying to continue to service as many of our existing customers as we can reasonably. This enables them to plan administration for their pool of needy patients. It also allows these to budget appropriately. They have relied on us for their immunoglobulin over the years, are familiar with the product, and we are confident that they will use it responsibly. These organizations are dealing with patients in critical need every day, and we believe that they are in a better position than we are to make judgments about how to distribute Sandoglobulin among their patients.

4.) Since October of 1997 we have been exclusively drop-shipping the product to end-users. We hope to minimize the development of secondary markets.

5.) In December 1997, prior to the FDA's request to companies to do so, we voluntarily established the Novartis Sandoglobulin Emergency Hotline. Through this program, we have set aside an amount of Sandoglobulin (at least 15 % of our available supply) to be available to any patient whose doctor will certify that the patient has a life-threatening need for immunoglobulin. Unfortunately, we are not able to satisfy the enormous number of eligible requests coming into the hotline (over 1000 calls per week). We have made a number of adjustments to the program to make sure that as many people have a chance to get some of the available product as possible. Through this program, about 3100 patients have received Sandoglobulin on a next day basis. Many of our staff have worked tremendously hard on this program, and, due to the tremendous strain on our internal resources, we have turned over the shipping of product for these patients to a specialty distributor (NSS – a division of Cardinal). All incoming calls are still managed by Novartis personnel.

6.) We are not supporting any new clinical trials during this period, although that is unfortunate.

7.) The Novartis sales force is not actively promoting Sandoglobulin.

As we have stated, Novartis is taking this shortage extremely seriously. We have requested more Sandoglobulin from the ZLB and, as distributors, are committed to ensuring patients receive this product as expeditiously as possible.

What Can Be Done to Alleviate the Shortage

We believe that, once the U.S. manufacturers are back in full compliance with FDA regulations and able to produce at prior levels, the shortfall in the U.S. market can be fully overcome.

In the interim it may be useful to examine:

- Importation of derivatives from plasma from non-U.S. donors manufactured in the rest of the world. This would involve extensive FDA review of offshore plasma suppliers and manufacturers.
- Re-examining the criteria for CJD withdrawal to ensure that all of these are appropriately balancing risk versus accessibility.
- Continuing to encourage rapid regulatory review of product lots for release and facility validation.
- Continuing to encourage restraint in the use of IGIV through the development of expert consensus guidelines.

Novartis Pharmaceuticals Corporation will work diligently with this Subcommittee to be part of the solution to this serious problem.

Mr. SHAYS. I thank you very much. One of the things coming through loud and clear is that the Red Cross sees CJD as a bigger problem for them, than the private manufacturers who purchase their blood supply. Is it conceivable that part of this is that ZLB maybe uses larger pool sizes? Is there a reason for what we're seeing? There must be a reason, and I'm not quite sure what it must be.

Dr. DUNSIRE. I'd like to take a crack at that, and I'm sure the American Red Cross will do the same.

Basically, the unpaid donors are generally older than the paid donors are, and therefore, given that CJD is a disease that manifests with age, we would find more CJD patients. In addition to which, human pituitary derived growth hormone hasn't been used in a while since recombinant growth hormone became available. So, it's more likely that an older patient would have received such an injection of growth hormone which puts them at-risk for CJD.

Mr. SHAYS. So, someone who has the growth hormone is viewed at-risk, and then, that whole pool is considered at-risk?

Dr. DUNSIRE. At-risk, and destroyed.

Mr. SHAYS. We had a hearing on this issue, and I had forgotten about that aspect of it. And the requirement now is that it be destroyed in what period of time? The pool——

Dr. DUNSIRE. I don't know the answer.

Mr. SHAYS. Does anyone know?

Mr. MCDONOUGH. If the donor, the difficulty is that these donors recall that on some prior time, they may have taken a growth hormone. And what we have to prove through medical search is that it was or was not human derived. If it was a recombinant product, it is permissible then, to use this product.

Mr. SHAYS. If it was what? I'm sorry.

Mr. MCDONOUGH. Human derived, as opposed to recombinant derived.

Mr. SHAYS. Recombinant would be OK?

Mr. MCDONOUGH. Recombinant is OK. And the difficulty is that very often, going back into the historical records, it is not very clear or we can't get documentation that it was or was not human or recombinant. In which case, if you can't prove the negative, then the material has to be destroyed.

Mr. SHAYS. Destroyed in what period of time?

Mr. MCDONOUGH. Any material that is—what happens is that the donor will come——

Mr. SHAYS. Once you have determined that it is a potentially at-risk pool, can you store it for 10 months or does it have to be destroyed. I think I remember someone saying 2 days, and that's what confused me.

Mr. MCDONOUGH. For point of clarity, what happens is a donor will come in and now that we have new criteria as of a year ago, we're asking these new questions. They're confronted with a question for the first time, or they didn't realize it was there 6 months ago, and they'll go home and they'll be told by someone, well, you did have a growth hormone. The donor will call us back, and we'll see that over the last year or two, they have made multiple donation, or in the last year, they've made multiple donations. We then have to track all those historical donations to see if any of that ma-

terial is in process. And if it's in process, all that has to be held in quarantine. And if we cannot prove that it was not human derived or a similar criteria for a duramater transplant, then all that material in quarantine has to be discarded.

Mr. SHAYS. I'm sorry. I'm going to be willing to have my staff weigh in here, because I just want to sort it out, and I don't want to be, because of my lack of knowledge here, just make it more confusing. So, the question is when does the blood supply have to be destroyed? Because my understanding is under certain circumstances, a pool at-risk can be sold provided it is identified that it is a known CJD potential; and having potentially affected this pool supply, the person can knowingly buy it, and you don't have to destroy it. Is there anyone here, or can any of the three of you respond to this?

Mr. MCDONOUGH. I don't think I understand——

Mr. SHAYS. I'm going to allow Cherri Branson to say what she thinks, and then allow anybody's staff to step in, and we're going to sort it out, because I've confused myself, and they've helped. [Laughter.]

Ms. BRANSON. Thank you. Let me, if I can clarify it. I think a part of the question, at least is whether the CJD—how long does the process take? It takes 180 days for production. Is that basically correct?

Mr. YETTER. It's variable.

Ms. BRANSON. And then, after that production process, there is another whole process. At which time, does the product go straight to market?

Mr. YETTER. The product would be produced then held for validation and then released.

Ms. BRANSON. How long does the validation hold?

Dr. DUNSIRE. That's usually very brief. It's merely a question of quality assurance at that point.

Ms. BRANSON. OK, now. I'm sorry, go ahead.

Dr. DUNSIRE. The big issue is the bits that are actually in the manufacturing process also have to be discarded. So it's not only final product.

Ms. BRANSON. And so they're dealing with the final product aspect. Once you determine that you're making some CJD contamination, do you destroy it immediately?

Mr. YETTER. Yes.

Ms. BRANSON. Immediately. So, I think a part of the question goes to the warning label issue. Is there any place either in the United States or internationally, where warning labels are used, and the product is sold with the consumer's knowledge that CJD may have affected the batch?

Mr. SHAYS. Let me just say, I'm getting the sense that the manufacturers were the ones we could have probably addressed this to. But they didn't make the issue that you are, and that's the troubling thing. You're making the issue of CJD, and we probably, if Mr. Wager were here, he would be able to jump in and tell us we're all screwed up.

Mr. MCDONOUGH. To our knowledge, there are no U.S. manufacturers or distributors of the product who will distribute currently a batch so-labeled as risk, because it sets up two different quality

levels of products. And there are certain product liability issues. There are customer issues, and there are some FDA guidelines where it constricts the availability for doing this as well.

Mr. SHAYS. Let me ask you this. Is anyone who testified before or who was sworn in as an accompanying witness, able to answer the question that we've asked? Mr. Bacich, why don't you come right up. I appreciate you, and maybe you can just be prepared to participate in this since you are a producer and it would be helpful.

Dr. DUNSIRE. May I make a comment, Chairman Shays?

Mr. SHAYS. Sure.

Dr. DUNSIRE. I think the reason it hasn't come up until this panel, is because of the much larger impact of this donor, unpaid donor plasma.

Mr. SHAYS. Well, I agree. And that part I understand. I understand that about the unpaid donor, and we seem to have a bigger problem here. It's just a coincidence that you all came last, but we wanted to have the Red Cross—I guess it wasn't a coincidence. But it's an issue we need to address. Yes?

Mr. BACICH. Is the question is there anywhere——

Mr. SHAYS. Let me just start from scratch here. We're talking about CJD, and I just need to know when you have to destroy pools—that basic—when you have a pool that's viewed as contaminated, potentially contaminated, what are the requirements for a manufacturer?

Mr. BACICH. First of all, once you're notified that a donor is in one of the high-risk categories, you have to take immediate action.

Mr. SHAYS. Right.

Mr. BACICH. Which means, when you talk about this 180-day process, you may have product in a variety of stages. So, it could be in plasma. It could be in a plasma pool. It could be in one of the fractionation intermediates, or it could be in finished product or it could be in the field.

Mr. SHAYS. Distinguish between plasma and plasma pool? I'm sorry.

Mr. BACICH. It could be in the individual unit sitting in your freezer.

Mr. SHAYS. And that's easy if——

Mr. BACICH. That one's simple.

Mr. SHAYS. And the ideal thing is to identify an infected plasma before you put it into a pool.

Mr. BACICH. Exactly.

Mr. SHAYS. OK.

Mr. BACICH. But, as Mr. McDonough mentioned, the difficulty is, particularly, if you have a donor, who either didn't understand the question or a family member 6 months or worse than that, a year or two down the road says you did have growth hormone, now that particular donor could be, particularly if it's a frequent donor, could be just about everywhere. But at the point where you have confirmed that it is a high-risk donor, you need to initiate the recall or destroy the product immediately.

Mr. SHAYS. OK. Thank you. All right, don't go anywhere. If you don't mind just staying. Do you mind? No. We go from the unit of blood to the pool, and then it's intermediate. What is the intermediate?

Mr. BACICH. The current process, and you've heard the term fraction 2——

Mr. SHAYS. So now, you're dividing it out?

Mr. BACICH. As you divide it out, those are termed intermediates.

Mr. SHAYS. Yes, OK. And then, you still have the product in part, and now the product is ready to sell—I mean ready to distribute. And eventually the product is going out of the plant.

Mr. BACICH. That's correct.

Mr. SHAYS. So by the time you discover CJD, and it's already part of the pooling, you've gotten down to what was an appropriate pool size. And I realize that different manufacturers have different pool sizes. But, there was this general consensus from our last hearing that we were going to try to get that number down to about 60,000. I guess one of the questions I should have asked Mr. Wager, would have been, whether one of the reasons, in addition to the issue of being elderly and so on, is that his company uses a larger pool size, and, therefore, it's at greater risk. But let me just get to this point. You have the product in the plant. It's ready to distribute. How long does the product usually stay in the plant now? What's the turnaround? How soon does it stay?

Mr. BACICH. The total elapsed time will vary from manufacturer to manufacturer. So the range is probably 150 to 200 days.

Mr. SHAYS. No, I'm not talking——

Mr. BACICH. In the final form?

Mr. SHAYS. In the final form in your plant?

Mr. BACICH. Typically, in final form the product is packaged, and at that point, the longest term test going on which is generally the sterility test, so product in finished form shouldn't sit in your plant longer than 7 to 14 days.

Mr. SHAYS. OK. One of the things we do know is once it's out, and you have a recall, it gets consumed pretty quickly.

Mr. BACICH. It does. That's why the discussion this morning on expiration date, a product with an expiration date of 2 years, I would venture to say that over the last decade, I doubt that any product has been discarded because it exceeded its expiration date.

Mr. SHAYS. Right. I hear you on that. So now we're back to this issue. When we know that CJD is a potential infectant to this pool, we have testimony that indicates in some cases that it's sold, but identified. Just maybe walk me through that. Do you have to get special permission? Are you destroying it?

Mr. BACICH. We have destroyed any product that has been returned, and I think there was testimony this morning that said there isn't a lot of product that comes back in these withdrawals. But, any product that comes back to us, is destroyed. Any product that is in final form awaiting shipment is also destroyed.

Mr. SHAYS. OK, then I misunderstood something earlier. Because I had heard in the hearing today, that there were instances where people knowingly purchased a product that had a potential of CJD infection.

Mr. BACICH. I think there was one case or two cases, with one of the manufacturers that did distribute the product with some special labeling because they had some high-risk donors in their pool. But, that's the only case that I'm aware.

Dr. DUNSIRE. It's my understanding that it was Alpha Therapeutics, and they distributed product in which albumin had been used, I think as an excipient, and the product had not yet been released from their facility. So it wasn't the IG fraction that had the risk of contamination, it was the albumin fraction which was separate. And that is used in excruciatingly small quantities, as in excipient in the process. The batch was still totally in the Alpha facility, and had not yet been released to the market. And under those circumstances,

Mr. SHAYS. It wasn't immune globulins?

Dr. DUNSIRE. Sorry?

Mr. SHAYS. It wasn't immune globulins?

Dr. DUNSIRE. It wasn't immune globulins, but the only piece that had any exposure to CJD was the albumin that was used in tiny quantities within the actual——

Mr. SHAYS. OK, and that was a very unusual circumstance?

Dr. DUNSIRE. Extremely.

Mr. SHAYS. Since you are back at the table here, you did not make a big issue of this—of CJD. I make the assumption that in terms of your operation, this was not a significant factor?

Mr. BACICH. The impact on Baxter, if you go back to about from 1996 on, the total impact was probably somewhere in the neighborhood of about 200 or 250,000 vials. And the reason for that, is at that time, recovered plasma is also available for sale in this country to be used as a commercial raw material. And this is plasma that is collected not in the Red Cross system, and we were using that material to help add to our plasma supply. And as you heard, the discussion earlier, the incidence of CJD is higher in that plasma for the demographic reasons that you heard about. But one other factor, I think, even if the pool size is the same, I think because of the donor volume, and donor frequency you need a lot more donations to get to a unit volume for processing. So the statistical opportunity to have a positive or high-risk is simply greater. And when you add the demographics to that, the opportunity is simply higher.

Mr. SHAYS. OK.

Mr. BACICH. Now, we since have stopped using recovered plasma, and have replenished our suppliable source, so the frequency has gone down. But at that time, it did impact us fairly significantly, but not at this time.

Mr. SHAYS. Thank you. You helped get us out of this confusion that I got us in. I think I have overload right now. But I do want to make sure that the record is clear. I'd like each of you to summarize, the three witnesses in panel four, for you to summarize your primary point, and then I may have a question to followup. If you don't mind just staying. And then, we may call it quits.

Mr. Yetter, you want to start out?

Mr. YETTER. Yes, Chairman Shays, it'd be fine. I guess from my perspective, my listening to the testimony all day, I think that the points that I would like to make is how responsible all the various partners, really in this process have been trying to respond to what is, indeed, a national crisis, and a problem. I think people have to be pro-active in trying to find the right solution. We discussed many possible solutions.

In my view, the most appropriate and important is really to get all of the suppliers up to capacity, overcoming any of the production problems. And we heard some optimistic reports that many of the companies are coming back, in terms of their capacity to supply the market. In the meantime, I think we need to continue those efforts to meet the needs of patients with the most urgent needs.

And finally, I think possibly the issue of CJD, but I would add my thoughts on that, in that, some of the words that were used earlier today about trust, and our confidence in product quality and all. I think before I would support any kind of step in the direction of having two standards of product or anything like that, I think, possibly convening an expert scientific panel to really try to understand the risk-benefit, but, my vote would be strongly against that, in terms of releasing any of that product that is potentially suspect at this time.

Mr. SHAYS. Thank you. All right, Dr. Dunsire.

Dr. DUNSIRE. I think the other thing that has been addressed today, and I would like to be very clear on Novartis' behalf, is that the medical emergency hot-line that we run requires no obligation from our customers. They never have to use Sandoglobulin, and they are not required to enter into any contracts with us.

Mr. SHAYS. Thank you for making that point.

Mr. MCDONOUGH. Yes. I think I would simply reinforce a few points. One, that each of the manufacturers, or several of the manufacturers had identified before the committee, their intent or actions currently pending to increase capacity, and any reinforcement that you can provide for that, and encouragement to the FDA to expedite the approval process is a helpful one.

Second, as we've just identified, CJ has more impact on the recovered providers of plasma product than the source providers of plasma products, and we maintain an acute interest in the safety of the supply. But relative to the HHS evaluations of this, we would certainly promote, relative to your point about labeling, a generic label of risk, rather than identifying individual lots or groups that may be at-risk because we just think that's an impractical solution in the marketplace.

And third, something to reaffirm I think, the point of view of the Red Cross that we intend to continue to invest mightily in research targeted to the transmissibility of CJD, and in derivative products, and hope that within the next 12 months, to have some definitive data to share with you.

Mr. SHAYS. I thank all of you. I would agree that the industry has made a very good case today, for where they find themselves. We never got into this issue, and I'm just simply not prepared to get into it, concerning how we determine the people most at-risk. We may have another hearing where we try to deal with that issue. I do think that there has got to be a way to recognize that if people truly are at-risk, and some are, that alternative uses have got to be looked at.

And I think that each panel provided a different view of this issue. So, it was very helpful and informative to the committee. Whatever my ignorance, my staff is listening more closely, and whatever we recommend, will be done in consultation with all who have participated in this hearing, because we do believe that safety

of the blood supply is paramount. We don't want to ever call into question the safety when, in fact, it is the safest in the world. And we do want to help the companies increase their production as quickly as possible, and as safely as possible.

I will be less inclined to recommend that we put into sale, any of the pools that have been called into question, but I don't think we will be pushing that as much. We will be pushing the research to try to get an answer to this issue, as quickly as possible. So we're weighing it that way.

And I thank all of you for being here. This has been a fascinating hearing, as have been others on the issue of blood and safety. Thank you so much.

This hearing is adjourned.

[Whereupon, at 4 p.m., the subcommittee adjourned subject to the call of the Chair.]

[Additional information submitted for the hearing record follows:]

MY LIFE STORIES

If I wasn't sick
and always felt well
I'd have my pick
of stories to tell.

Of birthday parties,
Of holiday fun,
Of sailing the seas,
Great times in the sun.

Instead my stories
are sad, but true.
They're stories of illness,
and feeling blue.

Hospitals
Shots
X-Rays galore
CAT scans and needles
Surgeries some more.

Doctors
Nurses
Syringes and pills
I.V.'s and gamma
Money for bills.

alpha®
THERAPEUTIC CORPORATION

IMMUNE GLOBULIN INTRAVENOUS (HUMAN) VENOGLOBULIN®-S 10% SOLUTION Solvent Detergent Treated

SAMPLE

Lot # GR7037A

The material contained in this lot of Venoglobulin®-S was manufactured with albumin as a reagent during the manufacturing process. This albumin was produced from a plasma pool containing a single donation from a donor at risk for developing Creutzfeldt-Jakob disease (CJD). This donor last received human pituitary derived growth hormone (HGH) about 13 years ago; the donor presently has no evidence of the disease. The known incubation period for acquiring CJD from HGH is from 4 to 30 years, but could be longer.

The incidence of CJD following HGH exposure is low. Also, there have been no confirmed cases of CJD transmission by HGH manufactured after 1977 in the United States. following introduction of an additional manufacturing step. The donor mentioned above was treated with HGH for one to two years beginning in late 1982.

Although there is a theoretical risk of transmission of CJD by plasma derived products, there have been no confirmed instances of CJD transmission in humans by blood or plasma products.

Studies with model agents for CJD have shown that these agents are reduced during certain manufacturing processes. Steps in Alpha's manufacturing process for albumin and IGIV are similar to the manufacturing steps shown to reduce the model agents for CJD.

Albumin is used as a reagent, and only trace amounts ($\leq$0.3%) of albumin remain in the final IGIV product.

The plasma used to make the Venoglobulin®-S itself was not derived from plasma associated with the pool containing plasma from the donor at increased risk for CJD.

The Venoglobulin®-S lot from which this vial was taken has been tested by Alpha Therapeutic Corporation and meets all quality specifications.

Immune Deficiency Foundation

IGIV Shortage - Physician Survey

John Boyle, Ph.D.

April 27, 1998

PHYSICIAN SCREEENER: DOCTORS, PATIENTS BY DIAGNOSIS

DIAGNOSIS	NUMBER OF DOCTORS REPORTING	NUMBER OF PATIENTS REPORTED
ATAXIATELANGIECTASIA	134	558
C1 INH DEFICIENCY	11	41
CD4 LYMPHOPENIA	6	10
CGD	234	841
CHEDIAK HIGASHI SYNDROME	2	3
CHRONIC MUCOCUTANEOUS CANDIDIASIS	160	1,070
COMPLEMENT DEFICIENCY	273	757
COMMON VARIABLE IMMUNODEFICIENCY	1,039	5,557
DIGEORGE ANOMALY	202	734
HYPER IGD SYNDROME	4	7
HYPER IGE SYNDROME	50	116
HYPER IGM SYNDROME	192	402
IgG SUBCLASS DEFICIENCY	799	5,307
LAD	17	30
SCID ADA	76	170
SCID OTHER	120	400
SCID X-LINKED	74	359
SELECTIVE IGA DEFICIENCY	936	5,502
WISKOTT-ALDRICH SYNDROME	142	388
X-LINKED AGAMMAGLOBULINEMIA	277	894
X-LINKED LYMPHOPROLIFERATIVE	7	16
OTHER	61	179
TOTAL	1,567	23,341

April 1998

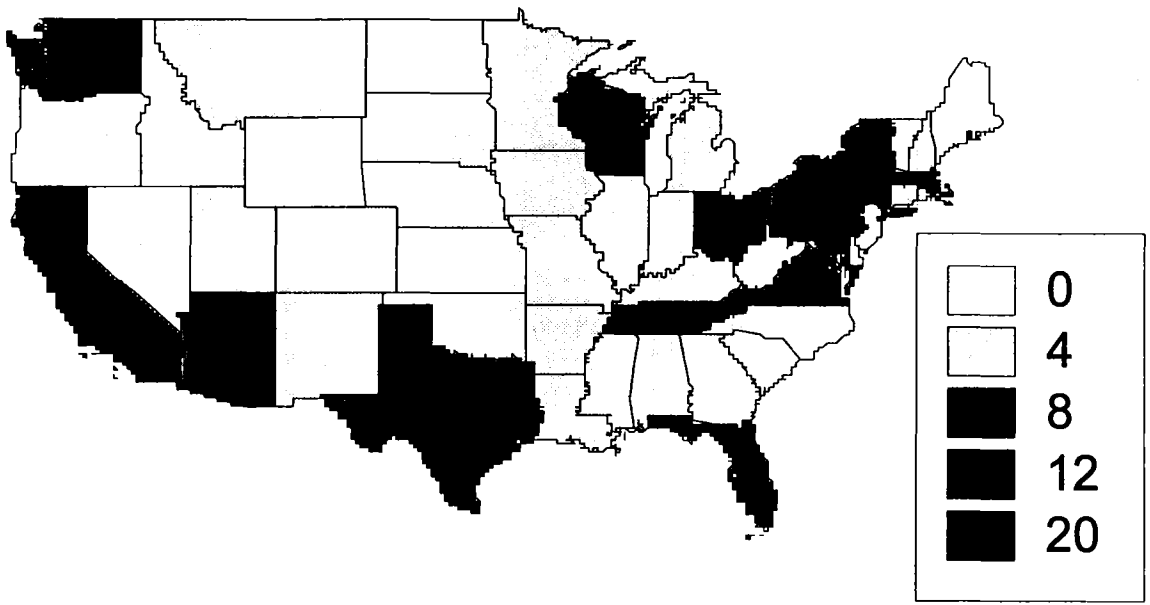
Physician by number of patients with primary immunodeficiencies

# of patients	# of physicians	total patients
25 +	221	15,044
<25	1,346	8,297
Total	1,567	23,341

Physician Survey Methodology

Physician Type	25 +	<25	Total
Drawn Sample	221	265	486
Completed Sample	147	101	248
Use IVIG	121	76	197

IGIV SHORTAGE - PHYSICIANS REPORTING



During the past six months, have you had any difficulty in obtaining intravenous gamma-globulin for your patients with primary immune deficiency diseases?

	Physicians 25+ Patients (N=121)	Physicians Under 25 (N=76)	TOTAL (N=197)
YES	93.4%	77.6%	87.3%
NO	5.0%	17.1%	9.6%
Blank	1.7%	5.3%	3.0%

NOTE: Yes includes 2 cases which left the question blank but reported problems subsequent questions and 4 cases which indicated no in Q3 but reported problem in subsequent questions.

As a result of shortages in IGIV supply during the past six months, which of the following (if any) has happened to you? (CIRCLE ALL THAT APPLY)

	Physicians 25 + Patients (N=121)	Physicians Under 25 (N=76)	TOTAL (N=197)
a) Had to contact new suppliers (e.g. pharmacies) to get IVIG	73.6%	48.7%	64.0%
b) Had to contact manufacturers directly to get IVIG	52.9%	25.0%	42.1%
c) Had to change usual IVIG product(s) used	86.0%	57.9%	75.1%
d) Did not receive IVIG orders from usual sources	60.3%	31.6%	49.2%
e) Received less IVIG than ordered	57.0%	35.5%	48.7%
f) Made special arrangements for access to IVIG supplies	55.4%	39.5%	49.2%
g) None of these	.8%	5.3%	2.5%
h) blank	7.4%	23.7%	13.7%

As a result of shortages in IGIV supply during the past six months, which of the following (if any) has happened to your patients? CIRCLE ALL THAT APPLY)

	Physicians 25 + Patients (N=121)	Physicians Under 25 (N=76)	TOTAL (N=197)
a) Postponed scheduled infusions	74.4%	57.9%	68.0%
b) Switched to different IVIG brand	81.8%	52.6%	70.6%
c) Switched to less preferred IVIG brand	65.3%	28.9%	51.3%
d) Interval between infusions increased	65.3%	40.8%	55.8%
e) Dosage at infusion reduced	50.4%	19.7%	38.6%
f) Unable to obtain product for indigent patients	22.3%	10.5%	17.8%
g) Substituted alternative therapies for IVIG	27.3%	3.9%	18.3%
h) None of these	1.7%	1.3%	1.5%
i) Blank	9.1%	25.0%	15.2%

To date, has the shortage of IGIV supply had a negative effect on the health of any of your patients?

	Physicians 25+Patients (N=121)	Physicians Under 25 (N=76)	TOTAL (N=197)
YES	51.2%	35.5%	45.2%
NO	40.5%	42.1%	41.1%
Blank	8.3%	22.4%	13.7%

How much difficulty are you experiencing now in obtaining normal supplies of IGIV products?

	Physicians 25+ Patients (N=121)	Physicians Under 25 (N=76)	TOTAL (N=197)
A lot of difficulty	47.1%	27.6%	39.6%
Some difficulty	38.0%	47.4%	41.6%
No real difficulty	5.8%	3.9%	5.1%
Blank	9.1%	21.1%	13.7%

Immune Deficiency Foundation

IGIV Shortage - Patient Survey

Preliminary Results

John Boyle, Ph.D.

April 27, 1998

Preliminary Results

IGIV Shortage - Patient Survey

- Mail survey to 800 patients (April 9, 1998)
- 158 Responses to date

Preliminary Results

IGIV Shortage - Patient Survey

- 158 Respondents
- 25 Do Not use IGIV
- 133 IGIV Users

Preliminary Results

IGIV Shortage - Patient Survey

- 133 IGIV users
- 26 (20%) Report no problem to date receiving IGIV
- 107 (80%) Report problems obtaining IGIV

Preliminary Results

IGIV Shortage - Patient Survey

- 107 Report problems obtaining IGIV
- 47 (44%) Report no adverse health effects
- 60 (56%) Report adverse health effects

Preliminary Results

IGIV Shortage - Patient Survey

- 60 Patients reporting adverse health effects
- 31 More infections and malaise
- 9 Adverse reactions to new brand
- 6 Pneumonia's, bronchitis and lung infections
- 7 Stress and anxiety
- 7 Adverse health effect not specified

Preliminary Results

IGIV Shortage - Patient Survey

Summary

- 80% of patients report problems obtaining IGIV

Of patients reporting problems obtaining IGIV…

- 56% Report adverse health effects (45% of all IGIV patients responding)

Carolina A1AD Support Network

Support for those affected by alpha$_1$-antitrypsin deficiency

1198 Big Branch Road, Clyde, NC 28721 704-627-2855

May 10, 1998

Rep. Christopher Shays, Chairman Subcommittee on Human Resources
B-372 Rayburn House
Washington, DC 20515

Honorable Representative Shays:

First let me thank you on behalf of all patients who use an intravenous plasma product. I recently had the opportunity to observe you conduct hearings on the IG shortage in the United States. I was most impressed with you and your committee's dedication to the patients needs and safety.

I am the Coordinator of the Carolina alpha$_1$-antitrypsin deficiency (A1AD) Support Network. A1AD is the most common lethal single gene defect of Caucasians in the United States. Nearly 100,000 people are believed to carry the severe form of the deficiency, yet only 5% are identified. This disease is as common as cystic fibrosis but because of its relatively new nature, it was identified in 1963, it is not well known nor understood by many physicians. It is virtually unknown by the general public.

Many of us are infused weekly with a plasma-derived product named Prolastin®. Our community has been affected by the many CJD withdrawals. We have also been affected by the present shortage. We live daily with a since of panic and dread. Dread, because we are afraid of all the unknowns associated with CJD. Panic because we are afraid that the drug that has been helping to keep our lungs from deteriorating further will not be available to us for our next infusion.

I had submitted testimony to Anne Marie. I am enclosing a copy of that for you plus some information on alpha$_1$-antitrypsin deficiency. Thank you again for all the help you are giving our community and those like ours.

For your convenience I can be reached at 704-627-2855. My email address is nabu@mindspring.com.

Sincerely,

Nancye W. Buelow
Coordinator of the Carolina A1AD Support Network and alpha$_1$ patient

Honorable Chairman and sub-committee members:

Thank you for allowing me the opportunity to testify before this sub-committee today. My name is Nancye Buelow and I have alpha$_1$-antitrypsin deficiency (A1AD). A1AD is the most common lethal single gene defect of Caucasians in the United States. Nearly 100,000 people are believed to carry the severe form of the deficiency, yet only 5% are identified. I am the coordinator for the Carolina Alpha$_1$-Antitrypsin Deficiency (A1AD) Support Network. I am here in the hope of putting a face from our community into the testimony of the plasma crisis we are facing in the United States.

The alpha$_1$ community consists of a group of children and adults that have a genetic liver disease. Simply put our livers do not produce the antitrypsin to protect our lungs. Many of us develop emphysema without ever smoking a cigarette. There is a replacement therapy available that is a human plasma derived product called Prolastin® made by Bayer. A majority of us are infused weekly with this product. There is no other FDA approved treatment available at this time. There have been many product withdrawals in the last three years due to possible CJD contamination. Many of us have been infused numerous times with the withdrawn product.

In my case the Prolastin® has stopped the deterioration of my lungs. Five years ago my pulmonary function tests showed 40% lung function. Recently my tests indicated that I had not lost any lung function since I began infusing Prolastin®. Obviously the product works, but is it safe? Are the FDA and the companies involved in plasma derived products doing everything possible to screen for CJD contamination? Our community does not need yet another lethal disease to worry about.

From what I understand there is no consistency at this time in product pricing. I also have been told that 50% all plasma collected in this country is sold overseas. This does not seem fair especially in light of the current crisis. Companies can not be allowed to take advantage of the shortage.

How can we avoid another plasma crisis like this in the future? Why are some patients receiving no product and some are receiving full doses.

The Veterans Administration and Military Hospitals seem to have the greatest difficulty receiving Prolastin® allocations. We have Viet Nam Veterans and their dependents that are not receiving Prolastin® at this time. This in itself is a travesty.

Although I am receiving my full dose I feel the need to speak up for those that are too sick to come before you today. There must be a fair way that product allocation could be enforced to follow the patient through. Some sort of identification number may help. Steps must be taken to insure our patient community, and those like ours, a safe and available product.

While I am aware that plasma is a commercial business in this country, there is a need for more public awareness into plasma donation. More people would be interested in plasma donation, if the FDA implemented a plasma awareness program.

I ask this committee, to please not fail our community and all the other patient communities that rely on plasma derived products.

Respectfully submitted,

Nancye Buelow
1198 Big Branch Road
Clyde, NC 28721

704-627-2855

Bushman, Jesse
From: LCStaples [SMTP:LCStaples@aol.com]
Sent: Monday, May 04, 1998 10:35 AM
To: Bushman, Jesse
Cc: LCStaples@aol.com
Subject: Attn: Anne Marie Finley – Critical Shortage of Immune Globulin

Thanks for helping us out. What follows is the text of a letter by Arnold Chait for incorporation in the record of the May 7, 1998 hearing of the Subcommittee on Human Resources:

Arnold H. Chait, Esq.
11 Dale Drive
Morristown, New Jersey 07960
Home: (973) 539-6683
Office: (973) 538-3800
Fax: (973) 538-3002

May 4, 1998
Via Electronic Mail
HR.GROC@MAIL.HOUSE.Gov

Anne Marie Finley, Subcommittee Staff
Subcommittee on Human Resources
Committee on Government Reform and Oversight
Congressman Christopher Shays, Chairman
B372 Bayburn HOB
Washington, D.C. 20515-6148

Re: CRITICAL SHORTAGE OF IMMUNE GLOBULIN

Dear Subcommittee Members and Staff:

Two of my children have a congenital immune deficiency. The medical diagnosis is Bruton's Agammaglobulinemia. This condition renders their bodies incapable of producing antibodies to infection. For approximately 16 years they have been maintained under a replacement therapy which requires that every four weeks they receive an infusion of immune globulin in large dosages. I have learned to administer these infusions myself, except for the period during which they are at college, where the college health center administers the infusions. Under this therapy, both of my sons have been able to live normal lives and to participate in the full range of academic, recreational and employment opportunities. However, our family is keenly aware that my sons are life-dependent upon these infusions and if they are not administered in a timely fashion, within a matter of days my sons can become critically ill.

During the entire 16 year period of the therapy my sons have received Sandoglobulin, a product which is distributed by Novartis in East Hanover, New Jersey, and made from human blood plasma. We have found Novartis to be a compassionate, responsive and reliable pharmaceutical company. We commend Novartis for its consistent sponsorship of programs which have directly or indirectly benefited our family and others dealing with primary immune deficiencies.

Over the last nine months it has become increasingly difficult to obtain this medication on a timely and reliable basis. We are aware that because of the unavailability of immune globulin from other sources, those in need of this medication have turned to Novartis. Extraordinary demands have

been placed on the Novartis product inventory, rendering Novartis unable to consistently supply immune globulin to patients who have regularly been maintained on Sandoglobulin.

In 16 years my sons have never had a reaction to Sandoglobulin and their health has improved significantly. There are medical implications of compelling patients like my sons to substitute another product as different medications can have varying effects and can cause reactions not experienced with Sandoglobulin.

In response to our past inquiries about the shortage we were advised that the pharmaceutical companies and the FDA were aware of this situation and that the shortage would be resolved in the near term. Within the last month, it has become apparent that the shortage has grown worse, no resolution is in sight, and we may be unable to get any medication. My sons' next dosage is scheduled to be administered on May 17th, 1998. All pharmacies, suppliers and hospitals that we deal with, including the National Institutes of Health, Bethesda, MD, (where the boys are clinically treated) report an inability to obtain adequate supplies of gammaglobulin (I.G.).

There is much speculation about the cause and responsibility for this crisis. While the affected patients and their families are interested in the inquiry into the causes of this crisis, of a much higher priority is the need for immediate action to assure that the lives of children like my sons are not at risk. The continued risk and disruption to their lives is inhuman and the anxiety is unbearable! We need confirmation that emergent action has been (not will be) taken so that with certainty those with primary immune deficiencies will regularly receive the dosages they need to prevent critical illness. It is simply unacceptable for the pharmaceutical industry and the FDA to announce that there is an inability to produce sufficient quantities of this medication to meet the needs of United States patients who are life dependent on IG. This crisis, although affecting a limited patient population, can better be assessed if one contemplates reading in next week's newspaper that pharmaceutical companies are unable to produce enough insulin to meet the needs of diabetic patients. Because IG is produced from donation of human blood, there is no issue of obtaining source materials as would be the case with medication produced from a Brazilian plant about to become extinct. Therefore management of this crisis is entirely within the capabilities of the pharmaceutical industry and federal health agencies and it is their responsibility to immediately resolve this crisis. I fail to believe that this country, with all its resources and technology, is incapable of allocating and distributing a blood based medicine in a manner which assures that sufficient quantities of IG will be available to patients who require this medication for survival. This crisis should be given no less attention than is given to national and natural disasters.

In an effort to assure that no other segment of our population which is life dependent on medication faces a similar situation, I offer the following recommendations:

1. The FDA or the Department of Health and Human Services should publish a list of all medications which are necessary to sustain life. Every manufacturer of these life sustaining medications should be required to project their manufacturing capacity and the foreseeable demand for each of these medications. By federal regulation a pharmaceutical company should be required to notify the FDA whenever it is likely that the demand for a medication will exceed its production capabilities. Delivery of this notification would authorize the FDA or other federal agencies to immediately conduct an audit of the manufacturing of the medication in question to determine:

   a. Increases or decreases in production
   b. Increases or decreases in product demand
   c. Analysis of distribution, including domestic versus non-domestic sales
   d. Changes in and adequacy of product inventories, including emergency supplies
   e. Utilization of production facilities and the ability to increase production
   f. Price changes

2. If as a result of the FDA audit it is determined that present manufacturing capabilities will be unable to meet critical patient needs, by federal legislation the pharmaceutical companies

holding patents or other proprietary rights to the life sustaining medication should be required or deemed to have granted a "license of necessity" to any other pharmaceutical company that is willing to undertake production of the medication. No claim of loss of proprietary rights can be asserted when the patent holder is unable to produce sufficient quantities of life sustaining medication to meet the critical health care needs of patients. In such a situation any potential loss of profits must be subordinated to prevention of loss of life. I request that your subcommittee oversee the mobilization of the federal agencies having jurisdiction to address as a national health crisis the unfulfilled needs of primary immune deficient patients for IG. Secondly, there should be appropriate inquiry to determine what needs to be done by way of federal legislation or regulation to assure that patients receiving life sustaining medication are not placed at risk of life because of deficient production, inventories and/or distribution practices of the pharmaceutical industry.

In my view the collective responsibility of the pharmaceutical industry extends beyond the development, manufacturing and marketing of beneficial medication. The pharmaceutical industry has a collective responsibility to forecast and monitor the market demand for life saving medicines to preserve life by insuring sufficient production capacity, reserve inventory, and priority distribution to meet the needs of the sickest patients.

Very truly yours,

Arnold H. Chait

AHC:beb

cc: Immune Deficiency Foundation
Congressman Rodney P. Frelinghuysen

marc ASSOCIATES, INC.

Shannon Penberthy

MEMORANDUM

TO: Anne Marie Finley

FROM: Shannon Penberthy

DATE: May 5, 1998

SUBJECT: NHF Statement on Product Safety and Availability

Per your conversation with Patrick Collins this morning, enclosed is NHF's statement on plasma product safety and availability for Thursday's Government Reform and Oversight hearing. Please let me know if you need additional copies or have any questions regarding the statement.

1101 17th Street, N.W. Suite 803 Washington, D.C. 20036-4704 202-833-0007 202-833-0086

STATEMENT ON THE AVAILABILITY AND SAFETY OF PLASMA PRODUCTS

Recently public attention has been drawn to the current difficulty of obtaining certain blood products, particularly intravenous immune globulin (IVIG) and clotting factor. While IVIG is primarily used by persons with immune deficiency disorders, persons in the hemophilia community who are HIV positive often use this treatment to prevent infection. The hemophilia community at large has experienced on-going shortages of certain Factor VIII and Factor IX blood clotting factor products and especially recombinant products.

People with hemophilia are dependent upon blood products to control their bleeding episodes, thus, shortages of clotting factor can be life threatening. Since the contamination of the blood supply with the AIDS virus in the 1980's, the safety of blood products has been an overriding concern for the National Hemophilia Foundation. Despite advances in manufacturing and in new clotting factor products, the hemophilia community and other users of plasma-based therapies remain susceptible to blood-borne pathogens and viral infectious disease. For this reason, blood product safety must be given the highest priority and consideration.

NHF recognizes that multiple factors contribute to the current shortages. Enhanced inspections of plasma manufacturing facilities by the Food and Drug Administration (FDA) over the last year have resulted in numerous citations and production shutdowns for failure to comply with good manufacturing practices. These actions are long overdue and necessary to improving the overall safety of blood products. Increased demand for blood products and international markets also have played a key role.

NHF is aware that the quarantine of plasma products suspected of contamination by Creutzfeldt-Jakob Disease (CJD) has contributed to shortages of certain products. The Foundation has worked with the FDA and the Centers for Disease Control to consider the evidence on CJD. NHF encourages the pursuit of improved information about the transmissibility of this fatal disease so that a definitive conclusion can be reached in determining whether these products can be released and safely used.

NHF and the hemophilia community remain committed to working with the FDA and with industry to address concerns about the safety and availability of blood products.

NATIONAL HEMOPHILIA FOUNDATION
116 West 32nd Street, 11th Floor, New York, NY 10001 212-328-3700 / 800-42-HANDI / fax 212-328-3777 / www.hemophilia.org

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9997 Laurel Street
Fairfax, Virginia
22032

May 6, 1998

To Whom It may Concern:

I was diaginosed with Common Variable Immunodifiency Disease in June , 1997 by Dr. Stephen Wienroth. I had been suffering from pneumonia and severe colds for several years. The Social Security Admisistration declared that I was disabled due to this disease. I am know collecting Social Security at age sixty -two. Since last June 13th I have been receiving gamma globulin as treatment for this aliment. The enclosed letter from Dr. Weinroth explains the symptoms and treatment briefly for the disease.

Last week, on " Sixty Minutes "

on CBS, I saw a program on the immune globulin shortage that exists in the United States. This shortage has been refered to me by my physician on several occasions. The CBS program indicated that the supply has been manipulated in the United States by several of the major producers. Studies at the University of Pennsylvania and Mt. Sinai Hospital were cited in this study. The leading manufacturers are exporting and selling at inflated prices the gamma globulin in foreign markets. It is being sold at 5x the US prices in the foreign markets. The major producers are Centeon, Alpha, Bayer, and Baxter. The gamma globulin is being produced from blood obtained in the United states and exported abroad. The existing shortage does not seem to be justified in any way. I hope you will help resolve this problem.

Hoarding and stockpiling cannot be justified with this medicine in ant way.

Respectfully Yours,

Robert S. Craig

cc. enclosure

Robert Scott Craig

Rep Shays

From: Mary Ann Crain
Sent: Tuesday, April 28, 1998 9:48 PM
To: Rep Shays
Subject: INTERVENEOUS IMMUNIGLOBIN - IVIG

Dear Mr. Shay,

I am a U.S. Citizen with a disorder known as hypogammaglobulinemia. This really means that I have a genetic immune deficiency. I was very ill from February 1993 until November 1996. Their were times my doctors did not think that I would live, and there were many times I felt so awful that I wished it too. They tried everthing they could think of and could not stop the infections and weskening of my body. Then I was diagnosed with an immune deficiency. They started IVIG treatment the very next day. It has been a very long uphill battle since then, but I can finally say that I am getting well. Without those treatments I can have no hope of a long life expectancy. The supply of IVIG in the United States has become critical. Many people are going without and are getting very ill. They need this medicine to survive. It isn't just a question of which medicine to give. There is no other FDA approved treatment for my disorder. Many people in the United States are depending on this medicine for their lives. Is it fair to ship our supply overseas when we are having a crisis here. I don't mind sharing a surplus, but why are we not helping our own first? As to the recalls, I for one would choose taking the small risk of getting some other disease if I had to choose between that and none at all. Everyone takes risks during their lives. Operations, transplants and many cancer treatments carry very substantial risks. That does not mean that we should refrain from the cure even though it carries a small risk. Whatever it takes we need to safequard our supply of this medicine for our nations needs. Any help you could be towards this effort would be greatly appreciated.

Sincerely,
Mary Ann Crain

Rep Shays

From: Julie Hamblen
Sent: Monday, April 27, 1998 3:26 PM
To: Rep Shays
Subject: Immune Globulin shortage

V0QK9MT1.doc

I am writing because I have Common Variable Immunodeficiency and must get IVIG every 4 weeks, otherwise I get severe infections. I am only 28 years old and I was informed last week by my Pulmonologist that I must get more frequent infusions due to lung damage from recurrent respiratory infections that have left me with lung damage.

There is a slight problem, there is a so called shortage right now. I get one story from my doctor and another story from Bayer the manufacturer of the IG I get. Last night I say 60 minutes and they did a story on the shortage. I was surprised to learn that the FDA has approved the sale of recently withdrawn product that was withdrawn due to increased risk for CJD to donors, and possible CJD resulting in death of one donor. Two years ago I recieved a lot that had been withdrawn, it took one year for me to be informed. Now I hear they are selling withdrawn product for a premiumn price?

Is this someone's sick joke, or is there a problem with the FDA. First the product is not fit for human use, now the FDA changes its mind and will allow the companies to release the product. Will patients know if they are receiving withdrawn product? Is there a liability of the pharm. company or doctor?

Anyway.. I am attaching the response I got from Bayer regarding the shortage, as usual they are blaming the FDA basically. You might find it interesting.

Sincerely,

Julie Hamblen

4 May 1998

Ms. Anne Marie Finley
B372 Rayburn House Office Building
Washington, D. C. 20515

Dear Ms. Finley:

Thank you for the opportunity to submit testimony for the hearings on 7 May 1998 on the shortage of blood plasma derived products in this country.

I am on the Board of the Alpha 1 Antitrypsin Deficiency National Association, and President of the Georgia State Chapter. My daughter is one of the 100,000 persons in this country believed to carry this lethal single gene defect. Presently only 5% have been diagnosed because this disease masks itself as asthma, allergies and chronic bronchitis.

This serious plasma shortage is deeply affecting the life of Alpha patients as well as, those in the Hemophilia and IGIV communities.

Thank you for allowing me to be heard. I am planning to attend the hearings on 7 May 1998 at 10:00 am. at the Rayburn House Office Building.

I am faxing this letter to the attention of Jesse Bushman at your office. For your convenience I can be reached at 1-800-725-7428 or my e-mail is { HYPERLINK mailto:alpha1-ga@worldnet.att.net }.

Thank you for your cooperation in all of this crisis situation.

Sincerely,

(Ms) Lou Glenn
President

1705-A Mt. Vernon Road • Atlanta, Georgia 30338 • (770) 350-6878
Fax (770) 350-6840 • 1-800-7-ALPHA-8 (800) 725-7428 (Outside Atlanta Area)

4 May 1998

Alpha 1 Antitrypsin National Association
Georgia State Chapter
1705A Mt. Vernon Rd.
Atlanta, Georgia 30338

Mr. Chairman, Members of the Sub Committee:

It is not only a privilege, but it is my obligation to speak before you this day and I thank you for the opportunity.

My name is Lou Glenn; presently I am a Board Member of the National Alpha1Antitrypsin Deficiency association; as well as, the president of the Georgia State Chapter

I come before you today not just as representative of these organizations, but, as a parent, One who was devastated when my 42 year old daughter was diagnosed with alpha 1 antitrypsin deficiency, a lethal single-gene defect. In 1992, the only article available to me stated " upon diagnosis the patient has approximately five years". As you or any parent would be, I was devastated. For as we all know, this is the wrong order of life. I questioned, how many more, where are they and is there any hope. ?

How many more? This disease that was thought to be rare a few short years ago is now believed to be as common as cystic fibrosis. By its very nature, patients are misdiagnosed with chronic bronchitis, asthma and allergies, more often than not, treated for up to 10-12 years without having the simple blood test that makes diagnosis possible. This late diagnosis leads to permanent lung damage and ultimately the lung transplant list. Our organization has a dual purpose in as much as we are responsible for raising the level of awareness in both the medical and lay communities and proceeding with our mission to Improve through education support and research, the lives of those affected by A1ad.

Where are they? Alphas have been found in every population except the Asian. Those from 22 countries on are the internet.

Is the hope? There is hope in a product, produced by the Bayer Corporation called prolastin. This Plasma derived product has shown in my daughter, as well as, so many others to result in fewer infections and hospitalizations. This means a saving on medical costs for both the government and the insurance industry. The five years alluded to in the first article is no longer true. Prolastin has enabled those in the alpha community to

live longer as productive citizens and able to fulfill their role as parents – the things most meaningful to each of us that we take for granted

Today we are confronted with a serious shortage of this plasma derived product. This is a critical time for the Alpha1 community, as well as, the Immune Deficiency and the Hemophilia communities. The shortage, not only deprives these people of what is in essence their life's blood, but raises their level of fear and anxiety which undermines the state of their health even further. Because of this shortage there are those who receive half the dosage prescribed. Newly diagnosed patients appeal to us when they learn this product is not available to them. I hear stories that pharmacies and/or healthcare companies make medical decisions on who gets product and who does not, and how much. Also of profiteering by wholesalers based on who will pay. All of which I find unconscionable

Additionally, distributors and pharmacies should notify users of withdrawals and recalls due to CJD and the like, to insure that the patient has a choice to accept or not accept product

Although I understand that research is moving forward in the area of CJD, there should be a standardized notification process which allows those with a dependence on biological products the opportunity to make informed decisions and to be proactive in protecting their own health,

Lastly, I pray that every effort will be made to develop recombinant products while insuring the safety of the biological products all these people depend upon.

Yes, I am here as a parent, but more important, as a human being. I ask each of you to employ all the wisdom and knowledge that has been afforded you, to take the action necessary to preserve the health and lives of all these people and all who follow in their path.

Thank you for your time and your attention.

End of comments.

Bushman, Jesse
From: Ted Gull [SMTP:gull@sea.gsfc.nasa.gov]
Sent: Friday, May 01, 1998 11:55 AM
To: Bushman, Jesse
Cc: gull@sea.gsfc.nasa.gov
Subject: Gamma Globulin Distribution has crashed: Life threatening issue

Jesse,
thank you very much for your time. I will compose a bulletized issue and recommended solutions for your consideration and send it via email over the weekend.

Ted

---------- Begin Forwarded Message ----------

Date: Fri, 01 May 1998 11:21:09 -0400
From: "Theodore R. Gull" <gull@sea.gsfc.nasa.gov>
MIME-Version: 1.0
To: rep.shays@mail.house.gov, gull@sea.gsfc.nasa.gov
Subject: Gamma Globulin Distribution has crashed: Life threatening issue
Content-Transfer-Encoding: 7bit

Congressman Shays:

I am writing to you because of the scheduled hearing next week on the availability of blood plasma products and distribution.

The distribution of gamma globulin has crashed in the past week; patients like me who depend upon the medication are unable to obtain it through normal distribution channels. And with the 60 Minutes article this past Sunday, I am very concerned that people like me are being held hostage by the FDA and pharmaceutical companies. Many lives are at stake and the problem must be fixed on the time scale of days to weeks, not over the next year as potentially indicated.

I am dependent on large quantities of gamma globulin due to a reaction to a flu shot over four years ago. After many experimental treatments by Hematology at Johns Hopkins Hospital, we determined that only a weekly treatment of 90 gms of gamma globulin and additional steroids could maintain my platelet level at 10 to 25K (where normal range is 150-450K).

My wife, who is a registered nurse, has worked with me such that we are able to infuse the medication at home, minimizing the cost wherever possible.

The issue is that the distribution of gamma globulin has crashed. Going through my home health services has been completely stopped. I am unable to obtain the medication through Johns Hopkins Outpatient services as previously since they too cannot obtain the product. Only by the Head of Hematology appealing directly to a local distributor have we been able to obtain about one month's supply, and we are told that the shortage will continue at least through the rest of the calendar year. Beginning last December, we found that the gamma globulin was in short supply; we responded by trying to stretch the interval, paying close attention to my platelet level. However, there is at this time no alternative treatment to maintain me, let alone provide a cure.

I plan to attend the open hearing May 7 that you are holding on this problem. Certainly the Associated Press article in the Washington Post this past Wednesday is highly inaccurate when they state that the product is readily available. The drop in complaints is due largely to the perception by the medical community and the patients that the FDA is not responding to the need.

As background, I am a PhD astrophysicist, having published nearly 200 papers in space science. I have fought this medical problem for over four years and am continuing to be productive, with over fifteen papers written this past year. I am contributing to society in a positive way and intend to do such in the future.

I am in contact with Senator Mikulski's office staff; they are working this issue with me. Hopefully I can contribute to information before, during or after your hearing. Please feel free to contact me.

Theodore R. Gull, PhD
9275 Brush Run
Columbia, MD 21045

Home: 410-381-8246
Work: 301-286-6184
gull@sea.gsfc.nasa.gov

———— End Forwarded Message ————

Theodore R. Gull, PhD
9275 Brush Run
Columbia, MD 21045

I am a patient critically dependent upon immunoglobulin in large quantities on a weekly basis. I have ITP (immune thrombocytopenia purpura) which was diagnosed in February 1994. Since then I have been a patient of Johns Hopkins Hematology and have undergone multiple treatments, some experimental, in an effort to control the problem and to correct the problem. The latter, I am afraid to say, has not yet been successful. Today I am here with a platelet count of 10-15,000 (where the normal range is 150,000 to 450,000). I am considered to be in a dangerous range, being at high risk to internal bleeding. I have a number of spontaneous bruises on my body at any given time.

My condition can be controlled with a combination of daily steroids and a weekly infusion of 90 grams of immunoglobulin. I have managed to stay out of the hospital since September, 1996. Rather I am receiving at home the immunoglobulin infusion, administered by my wife who is a registered nurse. Beginning early this past December, we suddenly could not obtain Gamimune but were able to obtain limited quantities of Sandoglobulin. We stretched the infusions to every ten days, even two weeks. The latter did not work as my platelet count dropped to below 8,000 and multiple, deep purple bruises appeared.

Two weeks ago, the distribution of immunoglobulin failed for me. The home health care provider suddenly was unable to obtain any immunoglobulin whatsoever despite efforts of buyers spending entire days on the telephone. With my doctor's encouragement, I began contacting the pharmaceutical firms directly only to learn that the shortage will continue for at least the calendar year, if not longer. We were able to obtain sufficient immunoglobulin to last me for four weeks, but it appears that the process will have to start over again in a few weeks.

Living with the day-to-day, week-to-week uncertainty of adequate immunoglobulin is extremely stressful and has greatly impacted my quality of life and ability to lead a normal life.

Two issues come out of this: 1) the FDA, while being quick to force changes in the processing of plasma products, has not considered the impact of these changes on the patients who rely on the immunoglobulin as a life-saving measure; and 2) the FDA has not informed the public in a timely manner that the shortage and distribution is indeed critical, and that the product should be reserved for patients in critical need.

Blood products are a life source for many patients like myself. We have encountered problems with the various products due to donors inadvertently transmitting life-threatening viruses. I applaud the FDA and pharmaceutical companies for correcting the processing to minimize these risks. However, there is no documented evidence that CJD has been transmitted via plasma products. I have to the ask the question as to whether the FDA has reacted too quickly to the detriment of patients.

In addition, it is unclear as to what is the actual supply of immunoglobulin.. is there hoarding, is there price gouging? These issues need to be investigated, clarified and corrected immediately.

Texas Children's Hospital

Located in the Texas Medical Center

6621 Fannin Street
Houston, Texas 77030
713/770-1000

Written Testimony for the Subcommittee on Human Resources, Committee on Government Reform and Oversight, United States House of Representatives by Karen D. Gurwitch, R.Ph., Pharm.D., Director of Pharmacy, Texas Children's Hospital Room 2154, Rayburn House Office Building May 7, 1998

Good Morning. Chairman Shays, Members of the Subcommittee on Human Resources, my name is Karen Gurwitch, Director of Pharmacy at Texas Children's Hospital in Houston, Texas. I am writing to you today on behalf of our hospital to impart our insight and experience with the recent intravenous immunoglobulin (IVIG) shortage affecting institutions across the United States.

Texas Children's is the largest free-standing children's hospital in the United States with 456 licensed beds. In fiscal year 1997, approximately 115,000 hospital admissions and an equal amount of outpatient office visits occurred at our facility. Of this patient base, Texas Children's provided primary care to approximately 90 immune deficient patients -- children with HIV, idiopathic thrombocytopenia purpura (ITP, a bleeding disorder), and patients receiving high dose chemotherapy associated with bone marrow transplantation. Other infectious diseases and illnesses benefitting from the use of IVIG, including Guillian Barre Syndrome, Kawasaki's disease are also treated at our Hospital.

In November 1997, our contracted provider was unable to provide us with our required monthly shipment of IVIG of 2000gm/month. By the first week of December 1997 we had only 200gm of IVIG on our shelves! This was a significant concern at our Hospital. If we were to treat an average size child (25kg. or 50lbs.) this supply would have allowed us to treat either 10 immune deficient patients for a single dose, or 2.6 children admitted with ITP, or five patients admitted with Kawaski's disease. At a national pharmacy meeting held in early December, I confirmed that this shortage was not an isolated incident, and that Texas Children's Hospital was one of many institutions struggling to maintain their IVIG supply.

While away, my Assistant Director was presented with the unenviable task of asking physicians to prioritize which patients required IVIG the most, because within two days there were more orders for use of the drug than available supply. Immediately, I began contacting local manufacturers' representatives and secondary wholesalers to educate them about Texas Children's Hospital's needs and to seek assistance in obtaining whatever immunoglobulin supply they had available. Primarily, I looked to companies we purchased other blood products from in hope that this pre-established relationship would support our ability to obtain IVIG. Some manufacturers were not interested in taking on "new, non-contracted" business. Fortunately, my perseverance paid off. Texas Children's did get backing (i.e., IVIG) due to significant purchases

of other products from these companies.

Additionally, the medical staff was asked to assist in identifying the best way to manage an IVIG shortage. Dr. Taber, the Chairman of the Pharmacy and Therapeutics Committee, asked key medical staff prescriber of IVIG and legal counsel to meet with the committee to determine Texas Children's approach in managing our vulnerable patient population during this crisis. Two approaches were considered: (1). To use up whatever supply we had on a first come first serve basis or (2). To develop criteria for the use of IVIG and reserve the supply for those indications that the subcommittee agreed were "priority." cases. Had we gone with the first alternative, based on our historical use of product, our supply of IVIG would have been expended within three weeks!

The ad-hoc committee comprised of physicians, legal counsel, and myself, developed a list of criteria patients needed to meet prior to receiving a dosage of scarce immunoglobulin. The members of the medical staff were informed of the criteria through a memo and the Hospital pharmacists "policed" all IVIG orders. Since our pharmacists and medical staff members were unaccustomed to utilizing strict criteria for the dispensure of a pharmaceutical, a peer review process was also initiated to ensure that physicians did not order the product and receive it, without regard to the shortage and to continuously monitor the modest supply of IVIG remaining. A peer review could be requested of the Chairman of the Pharmacy and Therapeutics Committee or the Director of the Pharmacy by the ordering physician. Since the shortage and the implementation of criteria and a peer review process, the use of IVIG at Texas Children's has fallen by 75% in the inpatient setting. However, our departments and physicians are operating under a "crisis mode" -- understanding that if they do not ration prescribed uses, our patients' health and well-being might be compromised, especially if this shortage continues.

Members of the Subcommittee, you all have heard through media and other coverage that the IVIG shortage began in November 1997. During that initial panic, the phone calls to manufacturers, secondary wholesalers, and even the FDA were abundant. However, as time has passed, hospitals, like Texas Children's, have learned to manage the small supply available. This, of course, has resulted in decreased phone calls, and perhaps a perception that the shortage is over. In fact, Texas Children's Hospital has managed a smaller than normal supply usually received. Finally, after several letters to elected officials and agency heads, news reports, and new hospital policies, Texas Children's received our November allotment of IVIG through our contractual agreement. Five months after the crisis began.

After conversations with several colleagues and learning about their inability to obtain this blood plasma derivative, I consider Texas Children's Hospital to be very fortunate. Since our initial scare, we have successfully managed the shortage in part through the development of criteria, a peer review process, and the willingness of some manufacturers to work with us until IVIG supplies are readily available.

Based on the experience of Texas Children's Hospital, I urge the Subcommittee to consider the testimony given at a hearing held by the Advisory Committee on Blood Safety and Availability on April 27, 1998 and April 28, 1998. In that hearing, we heard that the sale and distribution of

IVIG was increasingly being provided directly from the manufacturer to the health provider. This would enable better monitoring of supply and demand for this product, thus eliminating the potential for future shortages, price increases, and the operation of hospitals in "crisis mode".

I thank you for the opportunity to express my views and share the experience of Texas Children's Hospital with you regarding the IVIG shortage, and offer my assistance with the Subcommittee's task in any way.

Respectfully submitted:

Karen D. Gurwitch, R.Ph., Pharm.D.
Director, Pharmacy
Texas Children's Hospital

May 6, 1998

The Honorable Christopher Shays
United States House of Representatives
Washington, D.C. 22015

Dear Representative Shays:

On Thursday, May 7, 1998 at 9:30 a.m. in Room 2154 of the Rayburn Building, the Subcommittee which you chair will be conducting a hearing on IVIG.

As you know, recently "60 Minutes" aired a segment on IVIG and its high cost as well as limited accessibility except on the black market. IVIG infusions are vital to providing life for hemophiliacs as well as those who have ITP--Idiopathic Thrombocytopenia Purpura which is a virus resulting in the destruction of blood platelets. When the platelet counts drop to dangerous levels an infusion of IVIG (intravenous immunolglobulin) is mandatory. By receiving the IVIG, it fights off the destruction of the platelets and gives the body a chance of producing more in order for survival.

Representative Shay, I am writing to urge you and your colleagues to review this situation and make available IVIG to those in need at a rate that is within a families means and not $1000 per infusion.

In advance, thank you for your attention to this matter.

Sincerely,

Janet Gibbons Mariani

Janet Gibbons Mariani
Box 261
West Dennis, MA 02670

TO: Whom It May Concern

SUBJ: POETRY

FROM: SSgt Thomas F. McKinney, United States Air Force
on behalf of Amy Anthofer of Sarasota Fla.

I am sending this poetry written by Amy Anthofer who is 11 years old from Sarasota Fla. and must come to grips with not being selected in the LOTTERY process that has made her a number instead of a human being. Pain is felt by all of us in different ways and just for a second imagine the ungodly amount of pain she must go through, now knowing she was not selected and not understanding why she can't get the medicine she needs to continue living a "normal" life!!

To make a human life a number and say that's the best we can do is not acceptable and would not be something you could tell your child if he or she were in the same situation, I guarantee you.

Amy is one of the bravest people I have ever had the honor of knowing and **every minute** she lives, she cherishes.

Give her a chance to continue bringing happiness to the world.

Sincerely,

Thomas F. McKinney
1-703-588-6519 (W)
1-301-638-0790 (H)
mckinnet@af.pentagon.mil

Dear Mr Shay

My name is Dr Lacey Lewis, I have CVID. In the last 2 years I have been hospitalized 14 times. I fought my insurance company for 16 months to get approval. after only 3 infusions the Shortage began. I moved my family from Houston Texas to San Francisco in the hopes of better positioning myself for access to IGG. I have not had my infusions for 6 months and have been hospitalized 3 times for pneumonia.

I am the sole provider of 3 Children and my Alzheimers Patient father. I now am sick 4 days out of 7 with Spiking temps of 103. I live in fear that I may die soon and there is no one left to take care of my family. Please help me, and I would offer any help I can to the committee.

Dr Lacey Lewis
1803 VINEYARD AVE
ST HELENA, CA 94574
707-963-1823

local until Sunday
Washington Marriot
202-872-1500
Room 825

Alpha One Foundation

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† Executive Committee

* Denotes diagnosed
alpha$_1$ – antitrypsin deficient

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

SUBCOMMITTEE ON HUMAN RESOURCES

WRITTEN TESTIMONY BY

JOHN W. WALSH

ON BEHALF OF ALPHA ONE FOUNDATION

MAY 7, 1998

2937 S.W. 27th Avenue, Suite 302, Miami, Florida 33133
Telephone: (305) 567-9888 · (888) 825-7421 · Fax: (305) 567-1317 · e-mail: foundation@alphaone.org

Statement of John W. Walsh, President, Alpha One Foundation, before the Committee on Government Reform and Oversight, Subcommittee on Human Resources.
May 7, 1998

The Alpha One Foundation would like to extend its appreciation to Chairman Shays and the Subcommittee on Human Resources for holding these hearings and for focusing attention on the critical shortage of plasma derivatives upon which thousands of people afflicted by primary immune deficiency and alpha 1-antitrypsin deficiency depend.

The $alpha_1$ community embraces those families that are affected by the IVIG shortage. Similar to those afflicted by primary immune deficiency, individuals with alpha 1-antitrypsin deficiency depend on alpha-1-protease inhibitor (α1PI) to prevent lung damage from infection that causes the loss of lung function, disability and ultimately death.

This shortage exposes the tenuous nature of the thread between life saving therapies and the risk of death in these inherited disorders. The dependence of plasma derivatives as the sole option for life saving therapy demands constant vigilance by government, industry and the consumer communities.

This dependence further highlights the critical need for the NIH to promote the development of alternative therapeutic approaches to these disorders, including the need to develop new and more efficient delivery systems, dosing strategies and novel drugs based on DNA recombinant as well as gene therapy technologies. The timely application of new therapies can only occur in an environment that promotes the close collaborative effort of the NIH, FDA and the pharmaceutical industry.

In this context our elected officials must create the means for assuring safe, effective and accessible therapies for all Americans with these genetic disorders. Although the number of individuals on augmentation therapy for alpha 1-antitrypsin deficiency is relatively small compared to IGIV, 1 in 2,750 people in the United States is alpha 1-antitrypsin deficient . Consider that 1 in every 25 of your constituents is a carrier of the alpha 1-antitrypsin deficiency gene.

As a plasma derivative consumer, I know firsthand the helplessness that this shortage has created in my family and in our $alpha_1$ community. Since α1PI is available from only one manufacturer (Prolastin® by Bayer), the effects of the shortage are further exacerbated. An increase in raw material, in the form of IV-1 paste, is a limiting bottleneck in the availability of α1PI. I urge this Subcommittee to encourage other plasma derivative manufacturers to facilitate the sale of IV-1 paste to Bayer so it can increase and maximize its production of Prolastin®.

As a member of the DHHS- Advisory Committee on Blood Safety and Availability (DHHS-ACBSA), I applaud this Subcommittee for supporting the creation of the Advisory Committee. As you have heard from the Surgeon General this morning, the DHHS-ACBSA submitted several recommendations to Secretary Shalala addressing the critical shortage of plasma derivative products. On April 28th, testimony was presented by medical experts, plasma derivative consumers, the Alpha One Foundation, the $Alpha_1$

Antitrypsin National Association, the Immune Deficiency Foundation, Committee of Ten-Thousand, National Hemophilia Foundation, National Hemophilia Federation, the FDA, the NHLBI and the plasma industry. We encourage this Subcommittee to support these recommendations.

On behalf of the alpha$_1$ community, I ask this Subcommittee to investigate and correct the inequities in the distribution of these life-saving therapies. Prolastin® is currently being allocated at 50% of historic purchasing levels to distributors and health care providers. Consumer groups have presented testimony that some distributors and health care providers stockpiled the product before the allocation, and are creating an increase in the shortage as they contract with newly diagnosed patients. The reality to our community is that supply will not meet demand until 2000-2001, with the availability of another product by another plasma product manufacturer(s). We ask this Subcommittee to encourage the FDA to expedite the trials and approval of the two α1PI products currently in Phase III trials and require, with regulatory enforcement capability, post market dosing studies to establish optimum therapeutic results.

Finally, in accordance with the DHHS-ACBSA recommendations, I wish to emphasize the importance of the following recommendations to our alpha$_1$ community:

- collecting and disseminating information on production, distribution and demand on a monthly basis,
- exploring methods to optimize and standardize allocation of available products in an equitable manner,
- discussing triage of specific plasma derivatives to targeted groups,
- exploring the reallocation of partially processed plasma materials to other manufacturers in order to optimize production,
- exploring labeling and disclosure strategies to increase product availability without compromising public safety, and
- exploring the impact of temporarily decreasing the exportation of plasma derivatives while they are in short supply in the United States,
- exploring strategies for the development of reserve supplies of plasma derivatives and for their equitable allocation during shortages,
- supporting the recommendation that the NIH immediately evaluate alternative dosing schedules and delivery systems for alpha 1-antitrypsin deficiency, including prophylaxis strategies and strategies for treatment during acute exacerbation of disease, and accelerate the development of gene-based products and gene-directed therapies for alpha 1-antitrypsin deficiency, and
- encouraging the industry to work with the FDA to expand capacity sufficient to meet anticipated demand for plasma derivatives.

We commend the Subcommittee on Human Resources for pursuing the facts about the cause of this shortage and its interest in taking every measure possible to prevent its reoccurrence. It is imperative that we all focus on finding solutions to this life threatening crisis and support the immediate collaboration of government, industry and consumer communities.

Thank you for your consideration.

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STATE OF CALIFORNIA—HEALTH AND WELFARE AGENCY PETE WILSON, Governor

DEPARTMENT OF HEALTH SERVICES
2151 BERKELEY WAY
BERKELEY, CA 94704-1011

(510) 540-3503

May 6, 1998

The Honorable Christopher Shaye, Chairman
Subcommittee on Human Resources
Committee on Government Reform and Oversight
House of Representatives
Congress of the United States
2157 Rayburn House Office Building
Washington, DC 20615

Dear Congressman Shaye:

I am writing as the Council of State and Territorial Epidemiologists (CSTE) Hepatitis Consultant regarding the issue of shortages of immune globulin (IG) on which your Subcommittee is hearing testimony this Thursday, May 7, 1998.

CSTE has an approved 1997 position statement on IG availability which I understand will be included in the record of your hearing on this topic. We commend CDC on its efforts to facilitate access to IG stocks during this longstanding shortage. We, however, continue to be frustrated by the absence of a long term solution to this problem and urge FDA and Congress to work to implement a long term solution as soon as possible. This solution may involve assuring a minimum supply of IG through the public and private sector until increased funding for population-based hepatitis A vaccination can be made available. Our perception also is that FDA could do more to work with industry to assure that a safe product is rapidly made available to the market.

As stated in the CSTE 1997 position, "It is unacceptable that unnecessary civilian morbidity and potential mortality due to hepatitis A continues because of this situation."

Sincerely,

Stephen H. Waterman, M.D., M.P.H.
State Epidemiologist

May 4, 1998

Send IG testimony

Christine E. Zarro
419 Chabela Dr.
Manhattan Beach, CA. 90266

Dear Representative Shays;

I am interested in finding out more information about the IVIG shortage. It is my understanding from what I have read in the newspapers that you have finished your investigation.

My son was injured in a water polo game a year and a half ago. Due to that injury he has developed a neurological disorder known as PANDAS. (Pediatric AutoImmune Neurological Disorders Associated with Strep). This disorder causes him to twitch and jerk, very much like someone afflicted with Tourettes Syndrome. Without the IVIG treatment his condition deteriorates to a point where he can't read (because his eyes twitch so severely he can't see the words), he is unable to write (due to the arms flailing and jerking). He needs assistants in performing the simplest tasks (brushing hair and teeth, feeding himself, bathing, etc.). Ask yourself, how would you like to be sixteen years old and have to have your parents help you bathe? With his IVIG treatment he lives a normal teenage life. The IG stops all of the involuntary muscle movements completely. Whereas we are not in any danger of him dying without the IG, the quality of his life will be destroyed without it.

Until November of last year we were receiving the treatments through his neurologist at UCLA medical center. But as of November they have not had any available to us. We have been told that all of their available IG is going to the AIDS clinic. Fortunately, I have been able to locate the IG at other local hospitals. But the cost has been much higher for our insurance company.

I know that it is politically incorrect not to be totally sympathetic to people suffering with AIDS. It is a terrible disease, and I am sure a horrible, painful way to die. But it is very difficult for me to accept that my child is denied treatment for his problem, a condition that was not created by any "lifestyle choices", while others who put themselves at risk are given treatment. I know this is an unchristian attitude, but when I see the look on my childs' face when I tell him we can't get the IG - I can not feel any other way.

I know that you personally can't really do anything to solve this problem. But in any situation, having as much knowledge as possible usually helps a person cope better. I am extremely hopeful that you will be able to forward information to me regarding your investigation and what steps are being taken to resolve this issue.

Sincerely,

Christine E. Zarro (310) 798-0614

Christine E. Zarro

CONGRESSMAN
CHRISTOPHER SHAYS
MAY 1 1 1998
BRIDGEPORT, CT