Testimony of

Dr. Edward Gomperts
Medical Director and Vice President of Medical Affairs
and Clinical Development
Hyland Division
Baxter Healthcare Corporation

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Summary

Good Morning. My name is Dr. Edward Gomperts. I am the Medical Director and Vice President of Medical Affairs and Clinical Development of the Hyland Division of Baxter Healthcare Corporation. In addition, I am on staff in the Division of Hematology Oncology of the Children's Hospital of Los Angeles.

In my testimony today, I want to leave you with four overall points:

- Baxter is committed to producing adequate supplies of the safest, highest quality plasma therapies in the world. Our therapies include coagulation concentrates used to treat bleeding episodes suffered by individuals with hemophilia; intravenous gamma globulin needed by persons, such as cancer patients with immune deficiency; and albumin which is administered to burn and trauma victims in hospitals all across the country.

- We carry out an extensive program of safety and quality management in all aspects of plasma gathering, processing, manufacturing, and post-marketing surveillance to ensure that our products meet our high standards of quality and excellence.

- While we believe that this program already assures quality, we are now instituting a series of steps that will further limit possible risks associated with large pools of plasma, and we will do so in a way that does not dramatically reduce the supply of life-saving products.

- Finally, we wish to add a caution: Restricting pool size is not a panacea. Limiting the number of donors may have untoward effects that we cannot now identify. In addition, restrictions in one phase of the complex process of developing plasma-based therapies might have harmful, though unintended, consequences in other areas.

Our goal, Mr. Chairman, is to protect consumers and to provide them with quality products in which they can have total confidence. Baxter's current products meet that standard. But we are also committed to doing whatever we can to advance the frontiers of quality in all aspects of our research, product development, manufacturing, and operations.

Background

Before providing the details of those views, let me introduce our company. Baxter Healthcare Corporation is the principal domestic subsidiary of Baxter International Inc. Through its subsidiaries, Baxter is the leading manufacturer and marketer of health care services and products -- including those derived from human plasma -- benefiting individuals in nearly 100 countries worldwide. It focuses its research and development programs on biotechnology, cardiovascular medicine, renal therapy, and transfusion medicine.

Recently, Immuno International became part of the Baxter family of companies, and the combination of the two organizations will continue the long record of scientific and medical leadership that each has compiled.

I am pleased to have the opportunity to provide the Subcommittee with an update of the progress that our industry generally -- and our newly combined companies specifically -- have made in providing patients in this country and around the world with an adequate supply of technologically innovative, effective, and therapeutic proteins.

Baxter Focuses on System-Wide Quality

Let me begin by saying that plasma derived therapeutics are safe. However, speaking as a physician, the reality is that no useful medicine is without risk. The only way to guarantee 100 percent safety of blood or its components is not to use them.

We at Baxter strive to achieve maximum safety and efficacy for our products, and we focus on patient welfare. We try, we learn, but at times we make mistakes. The FDA, our competitors, this Subcommittee, and outside critics help keep our eyes on the target of patient welfare. Before changing well-established processes, however, we must guard against making choices for the wrong reasons. Science, reason, and patient welfare should dictate what we do, not political pressure, not media scrutiny, and not a desire for profit.

Baxter firmly believes that ensuring patient access to the highest quality plasma protein therapies requires that the entire system of producing these therapies be subject to continuous improvement, as well as to careful and constant examination. We believe this will let us be absolutely certain we are doing the most that human knowledge allows to ensure both safety and quality.

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For that reason, Baxter carries out a comprehensive quality and safety initiative (which I will highlight later in my testimony) in all phases of plasma gathering and product development -- including selection of the donor, processing of the plasma, inactivation of enveloped viruses, and post-marketing surveillance of the therapies we produce.

In real-world terms, that means our products are safe -- as safe as any medicine can be -- and that consumers can use them with confidence.

But we are also committed to finding even better answers for the future. For that reason, our quality program also includes development of entirely new technologies. Baxter is currently participating in research and development of technologies designed to provide further steps to inactivate viruses even before plasma is pooled, replace donated proteins with synthesized proteins, and provide genetic solutions to inherited conditions.

All of these efforts, together, reflect our view that true quality emerges not from a single factor, but from a comprehensive program that focuses on improvements in all areas. We believe this is a key point to keep in mind as the Subcommittee considers the question of pool size and its relationship to quality and safety.

Baxter Takes Steps to Reduce Donor Pools

On that issue, Mr. Chairman, let me say that we understand the concerns expressed by this Subcommittee and by the FDA about the size of plasma pools used to develop plasma derivative therapies. We take these concerns very seriously and appreciate the opportunity to discuss them with you today.

Baxter has re-examined its production processes and continues to debate whether the number of donors per pool has a significant relationship to safety. Frankly, we see no evidence to indicate that there is a safety issue linked to pool size, but we have no clear answer. Nevertheless, as a result of inquiries from the Subcommittee and the FDA and because the optimal number of donors in a pool remains an open question, we are taking a number of steps to reduce the size of the donor pools we use.

These are steps that can be implemented in short order, without lengthy review by FDA or massive redesign of our manufacturing process and facilities. Just as importantly, these are steps that will also allow the production of an adequate

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supply of the full range of therapeutics without threatening their potency or stability.

The steps we will implement include the following:

- Baxter will no longer re-pool -- or combine -- small quantities of plasma material from different production runs. We have done this in the past to conserve and ensure maximum utilization of these life-saving therapeutic proteins.

- We will substantially reduce repooling of small quantities of plasma material from various production runs that had been rejected because of problems with their packaging. Note that these materials were not rejected because of concerns over safety, but because of such things as misaligned labels. Nevertheless, this change is useful in that it will allow us to maintain the identity of the plasma pool and track donors more easily.

- We will revamp our production procedures to draw the active protein for a specific therapy and the albumin we use to stabilize that protein from the very same plasma pool. Our target is to do this in at least 85 percent of the production. This will, in effect, reduce the number of donors in the pool for these products.

- We will adjust our inventory and process control procedures to set an upper limit on pool size -- as measured by the number of individuals donating units to the pool. This will be done on a per-product basis and will maintain the identity of the pool through all stages of production. (This step is consistent with the proposed industry standard set forth by the International Plasma Products Industry Association.) We will ensure that no final product exceeds the donor exposure cap and many final products will fall significantly below.

  This initial target will result in an immediate reduction in potential donor pool size on the order of 40 percent for some products. The remainder of our products already fall at or below those levels. In addition, we will periodically evaluate and reduce these levels as manufacturing technology, clinical safety data, and regulatory considerations permit.

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Cautions About Inappropriate Reductions in Pool Size

After having summarized these actions, Mr. Chairman, I believe it is also important to add a couple of caveats with regard to limiting pool size.

First, we must be cautious about making radical changes. Our current manufacturing process was designed, validated, and licensed only after FDA reviewed our technical, scientific, and clinical data to be certain that the resulting therapies would be safe and effective. We were not permitted to distribute therapies from these facilities until we were able to generate data that convinced FDA that the resulting products met the standards of our license.

We do not now have the data on how radical changes in processing procedures might affect the safety or efficacy. Major changes in the process -- without FDA review and approval and without the supporting clinical data -- are not permitted, nor should they be. Because we are dealing in rare and fragile protein molecules -- which under certain circumstances can be rendered harmful to the patient -- we must avoid introducing unresearched and untested processing techniques.

Another caution to keep in mind as Congress contemplates limits on pool size is that there is a compelling human need for these therapies. Currently, Baxter facilities are operating seven days a week, 24 hours per day, and there is still unmet demand for some of our products. An international conflict that results in substantial loss of life or a major disaster could exhaust the current supply. Even under the most favorable conditions, building and licensing additional manufacturing facilities take upwards of three to five years before such facilities are capable of making, and are licensed to make, a meaningful contribution to the supply.

The point I am making is this: We must be certain that any efforts to limit pool size do not, inadvertently, increase danger for patients because they yield too little material to manufacture these life-saving therapies. Nor do we want decisions on manufacturing techniques to skew the product supply, safety, or efficacy needed by one group of patients to the detriment of another group. For these reasons, we look forward to working with the FDA to develop and implement a strategy that will allow us to continue to maintain practical pool size limits that will not undermine the equally important goals of ensuring access to an adequate supply of such therapies.

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In this same context, Mr. Chairman, I believe a word must be said about the complexity of the process used to develop blood-based therapies and how that complexity factors into the questions of pool size and possible limits on pool size. In addressing this point, I would like to provide just a bit of background about how the process of developing these therapies works.

As you may know, the basic materials used to develop these therapies are found in blood -- more specifically, in blood plasma. Once blood has been collected and the plasma has been separated, step-by-step we add progressively increasing concentrations of alcohol to the plasma to separate out the individual proteins -- or *fractions* -- of the plasma, such as albumin, gamma globulin, and clotting factor concentrates. This process is known as *fractionation*. We then use these proteins in producing our therapeutics.

Fractionation is a delicate and complex process. Proteins are separated in a specific sequence by varying such factors as temperature, acidity, speed of the centrifuge, and so on.

This is generally how the process works. The plasma material is mixed in a tank and is then processed through the centrifuges at a specific temperature, alcohol concentration, speed, and pH so that a specific protein can be collected. The remaining material is then reprocessed by adjusting the characteristics of the solution and centrifuged again to separate out a different protein. As minute changes of this type are made, each of the targeted plasma protein fractions is collected for final processing to constitute the licensed therapeutic.

The challenge for the fractionators -- those who perform this process -- is to separate the therapeutic proteins from the rest of the material, without altering the protein's beneficial properties, while concentrating them so that they can be administered to patients. But this is no easy task. These proteins are fragile and are often similar in structure to the substances from which they must be separated. Further, a slight variation one way or the other in a myriad of factors can result in a failed lot, a significant decrease in yield, and the loss of a significant amount of precious human blood components. Even worse is the potential to render a therapeutic protein ineffective or even harmful to the patient who receives it.

The point, simply, is that this process of fractionating plasma to obtain these important proteins is highly complex, comprised of many interlinked and interconnected steps. This process is unique to my company and the facilities in which it is performed, and this is true of the other fractionators as well. Major

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changes cannot be readily introduced in one step of the process, either upstream or downstream, without possibly affecting -- potentially adversely -- other areas. Even changes to enhance perceived safety in gathering one particular protein may reduce or eliminate another therapeutic protein -- thus harming other groups of patients.

Therefore, I return to the point I made a moment ago. Wholesale or dramatic changes that are imposed on this process -- including improperly designed limits on pool size -- can often boomerang, creating even deeper problems. We urge that all potential changes considered by this Subcommittee or FDA are given detailed clinical review so that we fully understand their impact before they are introduced.

Other Factors Besides Pool Size Are Critical in Safety

As Congress and FDA contemplate the question of pool size, we also ask you to take into account another important point: That is, safety and quality in blood-based therapies do not depend on the size of the donor pool, with the exception of the intravenous immuno-globulin product where larger pool size is needed. As we have indicated, this may be a factor. But a number of other elements in the gathering, processing, manufacturing, and production of such therapies and the materials used to make them provide the current substantial margin of safety.

I am pleased to report that Baxter carries out a comprehensive program to ensure quality in virtually every stage of this process. These include the following:

- QPP qualification of plasma centers. These are operating standards voluntarily adopted by plasma center licensees that are over and above the requirements of the FDA.

- Rigorous screening of all donors, including direct questioning and confidential exclusion of units from donors whose backgrounds may be of concern or in doubt.

- Testing all source material for Hepatitis B, Hepatitis C, and ALT and excluding any potentially harmful plasma from the starting pool and destroying those units. (ALT is a liver enzyme test that is a general indicator of liver function.)

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- HIV screening (ELISA) of every unit of plasma we receive, as well as excluding potentially harmful units from the starting pools and destroying them. This has occurred since 1985, including use of second and third generation HIV tests and combinations of tests.

- Special procedures -- called Lookback procedures -- to exclude from the starting plasma pool any units from donors who have subsequently tested positive on one of our screening tests.

- Comprehensive procedures to inactivate and remove viruses from the plasma. Baxter's Hyland Division introduced the first licensed, viral inactivated factor concentrate in 1983. This featured a heat method of virus inactivation. Subsequent refinements and additional technologies include monoclonal antibody affinity purification procedures, as well as other viral inactivation procedures, including solvent detergent treatment and vapor heating.

- Experiments being conducted to validate careful PCR screening of plasma pools to be processed and PCR testing of all batches of our therapies before they are released. PCR is a test that identifies certain sequences in the nucleic acids of specific viruses, rather than identifying antibodies that the human body prepares to battle the viruses. (Such antibodies are an indirect indicator of viral presences.)

In addition to these initiatives underway at Baxter, Mr. Chairman, I also want to outline the extensive quality system that has been in place at Immuno. This program has included placement of plasma centers in areas with low rates of potential blood-borne viruses, efforts to encourage repeat visits by well-qualified donors, comprehensive quality control auditing procedures, exclusion of questionable donors (including one-time donors), and special procedures to hold units in inventory longer, thus increasing the chances further that any potentially contaminated units of plasma will be detected and destroyed. On July 1, the members of International Plasma Products Industry Association (IPPIA) and American Blood Resources Association (ABRA) adopted a new voluntary standard which implements key aspects of this program, particularly the one-time donor exclusion, extended inventory holds, and PCR testing. These procedures are being adopted as rapidly as possible throughout the Baxter system and the entire industry.

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The results of these quality-control procedures, when fully implemented, are dramatic. Data from Community Bio-Resources, Inc. (CBR), an early adopter of these procedures and now a part of the Baxter family of companies, demonstrate the improvement in the margin of safety for plasma products. CBR plasma processed by Immuno showed viral reactive rates (per 100,000 donations) for the qualified donors for calendar year 1996 to be:

Viral Marker		Rate per 100,000 Units
(1)	HIV	0.26
(2)	HBV (hepatitis B virus)	0.66
(3)	HCV (hepatitis C virus)	1.05

In plain English, that means we found about one unit or less that carried these viruses in every 100,000 units of blood that were donated. Additional PCR testing of the last one million donations in the CBR plasma pools confirmed this low viral reactivity rate.

Keep in mind that this is even before further steps are taken to inactivate and remove viruses as the fractionation and production processes proceed. When the effect of these combined efforts are added together, it results in a very wide safety margin. Baxter and our entire industry are moving rapidly to implement this program through our systems.

In a nutshell, all of the statistics I've just cited mean that the plasma we use and the therapies we produce from that plasma are remarkably safe -- as safe as any medicine of any kind can be. As the Subcommittee contemplates the question of safety of blood-based therapies, we ask you to keep these results in mind. And we ask you to recognize, once more, that pool size issues must be considered in the context of the entire process of safety control, monitoring, and process management that we employ.

Baxter Views on CJD and Postmarket Surveillance

As part of our overall efforts to maintain quality and safety, post-market surveillance and recall of possibly unsafe product obviously play a key role. Let me briefly touch on those topics, before turning to questions related in particular to CJD.

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Each of the recalls that Baxter has carried out in the past has adhered to current regulations and has focused on the safety of the end-user, the patient. I believe our targets have been successfully accomplished, but – as in all areas – we seek to continually improve the process and are open to all meaningful and practical modifications or additions. We have been challenged by Dr. Pendergast of FDA to work together with the representatives of consumer and patient groups, and these interactions are taking place.

As you know, Mr. Chairman, the topic of recalls certainly relates to CJD and concerns over its possible presence in the blood supply. Because of those concerns, we have carried out five separate recalls so far this year because a plasma donor may have previously used autologous dura mater or received injections of human growth hormone. In each of these, we have sedulously adhered to the requirements for such recalls at all levels. Nevertheless, this issue has caused enormous consternation and fear among numerous users and beneficiaries of albumin, where the possibility of transmission of CJD is too low to be determined.

Ongoing epidemiologic analysis of sporadic CJD and its variant, both in the U.S. and Europe, continues to point towards food contamination and the ingestion of contaminated material as the key medium for transmission of a yet-to-be-identified infectious agent. In contrast, epidemiologic studies, both ongoing and completed, have not identified a blood mediated transmission mechanism to date. Completed, analyzed, peer-reviewed data from carefully conducted and appropriately controlled animal studies has yet to take place on this issue.

My own company is advanced in the development of a research study to be carried out on primates as well as mice, but time is a serious problem since it takes many months to develop a meaningful research plan, months to initiate the plan properly, and years to obtain the results. However, I fear that the blood-transmission issue is receiving more attention in this country than the food contamination problem.

Baxter and Plasma Industry Are Conducting Wide-Ranging Research

One of the clear lessons of the CJD issue, Mr. Chairman, is that we can never be content with the current state of knowledge of disease or the current capacity for ensuring high quality and safety. We must continue to seek new techniques and new strategies for reducing risks, enhancing safety, and improving the quality of plasma protein therapies.

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In effect, we must continue the progress that has occurred in hematology over the past 50 years. During that time, progress has been marked by utilizing technology to conserve the life-giving properties of blood and plasma and of administering ever more precisely the specific protein that the patient needs. In the 1920's and 30's, blood therapies consisted of whole blood or packed red cell transfusions. Then researchers discovered the ability to separate plasma from blood cells and, during World War II, to remove the albumin from the plasma. Still later, researchers discovered new fractionation techniques that allowed them to separate other proteins, such as coagulation concentrate and gamma globulin.

This entire process has rested on two very clear and very critical realities: First, therapeutic proteins come from the blood of ordinary citizens who are willing to give of themselves to aid their fellow citizens. These proteins are not found in isolation. Second, the progress we've seen of finding ever more precise proteins to better-fit the needs of patients relies upon this very complex, very essential process of fractionation that I described earlier -- as well as on the intensive research over the years that has increased our knowledge of this technique.

We are committed to the pursuit of continually improved techniques to continue that march toward safer, better protein therapeutics. All of this takes time and energy and effort, but those efforts have been worthwhile for they have borne clear improvements in safety and quality.

Now, Mr. Chairman, I would like to highlight a number of research areas that we believe are also critical steps for the future. Each of these initiatives offers the potential for enhanced safety and quality as they reduce risk.

A major Baxter initiative is Project Aegis. This is a comprehensive effort by Baxter's research staff and a panel of world class scientists to scout out potential threats of infections transmissible by blood or plasma, and to develop new technologies and techniques to detect, identify, and remove units of plasma possibly containing pathogens before they can enter the production process.

Its goals also include developing new techniques for viral inactivation or removal. Possible new approaches include nano filtration, a technique to filter out small viruses, and methods to inactivate small, non-enveloped viruses, which are highly resistant to our current inactivation technology. Various methods of photo-dynamic binding or destruction of viral and bacterial genomic nucleic acid are also being tried.

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In addition to this research, Baxter is seeking solutions for tomorrow in a number of other areas:

- Consortium for Plasma Science

  Baxter has taken a leading position in the formation and operation of the Consortium for Plasma Science, whose sole purpose is to identify innovative research on new technology that would inactivate viruses. This industry-supported collaborative research organization has allocated substantial seed money -- $20 million over five to six years -- to promote and fund research and development of new technology in the inactivation of viruses and other pathogens that might affect blood and plasma. Additional resources will be committed as circumstances warrant. A Request For Proposal was published early this year and multiple research proposals in response have been received by the Consortium. These are currently under evaluation by the Consortium expert scientific review committee. Successful technology will be licensed to all member companies and will be offered to other applicants.

- Enhanced PCR Tests

  Immuno has taken a leading position in the development of highly sensitive PCR technology to screen all donated plasma for the major viral pathogens -- HIV, HCV, HBV, and additional viral markers. New systems will be introduced as rapidly as possible. Baxter and Immuno researchers and technical staff are working with the FDA, other fractionators, and the American National Red Cross to obtain regulatory approval for licensing this PCR technology to screen plasma for known blood-transmitted viral agents.

- Recombinant DNA Research

  In 1992, FDA approved Baxter's Recombinate, the first genetically engineered synthetic Factor VIII, which is used to treat the most common form of hemophilia. We are now conducting research on the use of recombinant DNA technology to synthesize additional plasma proteins -- thereby reducing the need to rely solely on human plasma for therapies to treat patients with a variety of inherited conditions.

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- Blood Substitute

  Baxter is completing Phase III clinical trails on its virally inactivated, oxygen-carrying substitute for human hemoglobin. This will provide an alternative to whole blood or packed red cells in many treatment areas.

- Gene Therapy

  Baxter continues its research to find a genetic answer -- and hopefully a cure -- for inherited diseases such as hemophilia, thereby obviating the need for continued therapy. This is a potentially revolutionary approach with enormous potential. It would allow a physician to prescribe a treatment which -- instead of supplying the missing protein --would supply the needed gene so the patient's body could provide the needed proteins.

Conclusion

In conclusion, Mr. Chairman, let me reiterate that our company continues to be committed to making the best, safest, highest quality products. We are constantly seeking -- and are always open to -- suggestions that will achieve this in the most effective manner, both today and tomorrow.

But we believe that all efforts to achieve these goals must be realistic, must ensure an adequate supply of therapies for all patients, must recognize the extraordinarily complex process of developing blood-based therapies, and must be part of a comprehensive and long-range program that ensures quality today as it unlocks the mysteries of disease for tomorrow.

Baxter continues its goal of utilizing the best scientific research and the latest techniques to achieve quality and safety. We remain committed to a policy of critical examination of all processes we use, to continuous improvement of these processes, and to maintaining an open and frank dialogue with patients, doctors, FDA, and Congress as we respond to these scientific and medical challenges.

I thank you for the opportunity to share these views and developments with you.

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