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Summary

As shown in annual reviews by the National Swedish Board of Health and Welfare, Sweden has been self-sufficient in blood plasma since 1990. This investigation, which involved extensive collaboration with a range of interested parties, however, confirms that Sweden is facing a substantial risk that certain aspects of plasma collection will be discontinued due to price competition, primarily from the United States. Other European countries face a similar situation.

Discontinuation of current plasma activities would pose a serious threat to Swedish and European self-sufficiency. The goal of self-sufficiency in blood and blood products in the European Union, through voluntary, unpaid donation, was established by an EC directive in 1989, and has since been confirmed in several resolutions from the Council of Europe and the EU Parliament. However, the European Commission's statistics on collected plasma volumes and the use of plasma and plasma products show that member states are now further from the goal of self-sufficiency than they were in the early 1990s.

The Swedish National Working Group on Blood Self-sufficiency, chaired by Professor Lars Werkö, was appointed by the Swedish Ministry of Health and Social Affairs. In this report, the Working Group presents the findings from their investigation into issues concerning blood plasma supply. The Working Group suggests several measures which should be considered to ensure Swedish self-sufficiency and come closer toward achieving the goal of European blood plasma self-sufficiency. By definition, self-sufficiency implies a balance between the supply of source plasma and the demand for the plasma products manufactured from the

primary source. The Working Group analyzed and reviewed factors and conditions affecting both supply and demand.

The Importance of Harmonizing European Regulations on Plasma Safety

In the European Union, blood plasma intended for fractionation is a good which, in principle, should be permitted to move freely across borders between member states. Therefore, a basic premise in this investigation has been that Swedish problems can be neither analyzed nor addressed in isolation, but must be viewed in a broader European context. Likewise, self-sufficiency problems cannot be addressed separately from issues relating to the safety of blood and blood products.

A condition for self-sufficiency within the European Union is that member states are able to rely on the quality and safety of products produced in other member states. Such a level of confidence can be created only by harmonizing the regulations and routines concerning plasma safety. The Working Group believes that the recommendations (upon which EU's ministers of health recently achieved political agreement) addressing the selection of donors and the testing of donated blood is an important step in European harmonization. In the long term, the goal should be that all plasma products – whether manufactured within the EU or imported – must comply with the requirements specified by the European Commission, EU's Council of Ministers, the central pharmaceutical authority within EU, the European Agency for the Evaluation of Medicinal Products (EMEA), and the European Pharmacopoeia.

Testing the Regulations for Plasma Collection Volumes

Since the use of plasma products has gradually increased and reached levels which cannot be met by the plasma obtained from collecting whole blood (recovered plasma), the issue of self-suf-

ficiency has increasingly focused on the supply of plasma specifically from plasma donation (source plasma). The supply of source plasma is dependent on, e.g. access to plasma donors and the collection volumes allowed. In Sweden, access to donors has been relatively good. However, differences in regulations between Europe and the United States concerning the allowed collection volumes and intervals, presents a problem. To collect the same volume of source plasma, more donors must be interviewed, tested and collected in Sweden (and other European countries) than in the United States. This results in a significantly higher total cost per plasma kilogram collected in Sweden than in the United States.

It is the opinion of the Working Group that differences between U.S. and European regulations are not based on scientific knowledge, but have emerged from practical experience and local traditions, and are due to the limitations associated with the apheresis technique itself. This has previously limited the possibilities to individually adjust the collection volumes according to, e.g. the weight and gender of the donor. Today, the technical situation is considerably better. Hence, it is urgent to conduct a scientific study of the medical and economic consequences of alternative, more individually adapted collection routines. Since these issues are of great interest throughout Europe, the Working Group suggested in its background document to EU's Council of Health Ministers in June 1997 that such a study would receive financial support from the European Commission. The European Commission's Directorate General V (DGV) is intending to support such a study.

Cost-Effectiveness of Swedish Plasma Activities

The competitiveness of Swedish source plasma depends not only on local collection routines at plasma centres. A review of economic data from the collection centres indicates that there may be several possibilities to decrease the cost of production and improve competitiveness. A financial question, raised by the plasma establishments, concerns the interpretation of the Swedish VAT

legislation concerning county council sales of source plasma. Discussions with representatives of plasma establishments and the plasma industry indicate that the interpretation of the regulations is unclear. The Working Group's assessment shows that clarification on this issue is needed from the National Swedish Tax Board.

From an international perspective, plasma activities in Sweden are characterized by many, relatively small collection units. This is a disadvantage, e.g. in purchasing routines, when a small volume may cause higher unit prices for, e.g. test material. To increase safety and cost effectiveness, several European countries have centralized blood and plasma activities. Some discussions have also taken place in Sweden. Centralization may, however, cause problems concerning competency issues and efficient supervision of the remaining transfusion activities.

In light of the complex issues, the Working Group considers a national review of the structure, organization, and cost effectiveness of plasma activities to be motivated. Natural collaboration partners in such a review would be the Federation of Swedish County Councils, the National Swedish Board of Health and Welfare, the Medical Products Agency, and Spri. Since experience from abroad suggests that national reorganization may take several years, it is urgent to start this work immediately. As a result of discussions in the Working Group, the Federation of Swedish County Councils has already initiated the planning for such a review.

Regulating National Responsibility for Plasma Supply

Although over 90% of plasma collection is managed by the medical services, no regulations require the county councils to collect plasma which will not be used for direct transfusion to patients. If the collection of plasma for fractionation does not cover the costs, there is a risk that local decisions will be made to discontinue this activity, even though Sweden as a nation is committed to the goal of European self-sufficiency.

In 1985, the National Swedish Board of Health and Welfare was charged by the government to monitor progress toward increased

self-sufficiency in blood and blood plasma. This charge does not offer any real opportunities to govern apheresis activities. Today's problems were not apparent in the mid 1980s, and plasmapheresis activities did not develop on a larger scale until the late 1980s. The goal of European self-sufficiency as outlined by EC Directive 1989/381 had not been binding until Sweden entered EU. The role of Swedish authorities is complicated by the fact that the National Swedish Board of Health and Welfare supervises traditional transfusion activities, while the Medical Products Agency supervises the manufacture of blood components used as source plasma for drugs.

In light of developments during the past decade, national responsibilities need to be clarified, i.e. which body or bodies have the responsibility to ensure that Sweden as a member state in EU, contributes toward the goal of self-sufficiency, and which incentives or sanctions can be used to work toward this goal. The Working Group suggests that the National Swedish Board of Health and Welfare and the Medical Products Agency be charged with reviewing the legal base in Sweden for determining how national responsibilities concerning plasma supply can be best regulated.

A central issue in this context is whether the collection of plasma for fractionation – analogous with blood collection for transfusion – can be defined as a responsibility of the county councils. Collecting source plasma for pharmaceutical production is an activity of principally different character than local transfusion activities. There is, however, a strong practical link between these two types of activity. It must be considered that the end products manufactured from source plasma are an integral part of the treatment arsenal required to meet the population's need for medical care.

If collection of source plasma for drug manufacturing is defined as a county council responsibility, an objective must be optimal national coordination. Increased collaboration among county councils may be required to assure the quality, safety, and cost effectiveness of plasma activities.

Evidence-based Medicine and the Demand for Plasma Products

The use of end products manufactured from source plasma – especially coagulation factor VIII, albumin, and immunoglobulins – varies among EU countries, and even among different parts of Sweden. It is obvious that demand is driven largely by local and regional treatment traditions and routines. Although issues concerning the optimal use of plasma and plasma products have, to some extent, received attention at a European level, they have been of relatively low priority.

According to the Working Group's assessment, there is a major need to scientifically review the indications for utilization of these products. This need has been accentuated by the introduction of new, genetically engineered alternatives to plasma derived products. On the initiative of the Working Group, the Swedish Medical Research Council (MFR) has initiated planning for a state-of-the-art conference on the use of plasma products. In the European collaboration concerning self-sufficiency problems, Sweden should work toward attracting greater attention for issues concerning the optimal use of plasma products.

Future Perspectives of the Plasma Industry

For the Swedish plasma industry to survive, the manufacture of plasma drugs by fractionation must achieve profitability. According to the representatives of the pharmaceutical industry, the price difference between U.S. and Swedish source plasma plays a decisive role for the future. If higher collection volumes are allowed, the profitability of the plasma industry can increase and lower the purchase price for source plasma. The results from the planned European collection study will most likely influence the trends in this respect.

Industrial profitability also depends on how many end products can be gained from source plasma. Despite the belief of a few years ago that the growing demand for plasma products had reached its peak, production has increased. As a consequence of introducing

recombinant factor VIII, the demand for plasma derived factor concentrate has decreased. Concurrently, however, the use of immunoglobulins has increased.

Results from the planned state-of-the-art conference, and other initiatives to review and strengthen the scientific foundation for the use of plasma products, may influence future demand. The future may also hold entirely new plasma products and treatment opportunities. Despite the introduction of recombinant products, the current thinking is that some plasma derived products cannot be replaced by genetically engineered alternatives.

International Collaboration on Blood Issues

Many international organizations address issues related to blood and plasma donation and the use of blood and blood products. The WHO General Assembly, the Council of the European Union, the European Commission, the central pharmaceutical authority within EU, the EMEA, and the European Pharmacopoeia can make binding regulations and non-binding recommendations. Furthermore, e.g. the International Red Cross, the Council of Europe, and the International Society of Blood Transfusion (ISBT) have issued recommendations. There is, however, little regular official contact among the various authorities, which might guarantee consensus.

The regulations and many recommendations dealing with blood and blood plasma activities lead to a special observation. Instead of building on a systematic report of underlying scientific studies, most of the documents are based on consensus among high-level experts, and have not documented the current body of scientific fact. Often one group of experts refers to the next, the statements of which are either accepted without further review or slightly modified.

In future collaboration, the representatives from Sweden should attempt to ensure that the foundation for recommendations and regulations are reviewed according to the principles of evidence-based medicine. Consensus documents issued by experts – no matter how ”high” their reputations – are insufficient. Such documents should be accompanied by systematic reporting of scientific

facts, and be made available for external review. This procedure will increase transparency in decision making and concurrently facilitate effective updating of the respective documents.

Likewise, scientific demands should also apply to national regulations developed by public authorities. In the future, the best opportunities for influencing EU will probably rest with countries that can create effective mechanisms to rapidly develop a scientific basis to back up their opinions and decisions. The Working Group therefore suggests that the government commission the National Swedish Board of Health and Welfare and the Medical Products Agency to investigate the scientific basis the regulations addressing blood and plasma activities.

Highest priority should be given to reviewing the regulations affected by the new EU recommendations on selection of donors and testing of donated blood. Concurrently, organizational structures and working methods should be developed to scientifically monitor and take positions on closely related fields that are soon likely to be affected by EU collaboration, e.g. inspection and quality assurance of activities concerning blood and plasma.

1 Introduction

On February 6, 1997, the Swedish Government decided to appoint a Working Group to review Swedish blood plasma supply.(1) Professor Lars Werkö was appointed as Chairman and Pia Maria Jonsson, M.D., Principal Administrative Officer was appointed as Secretary. The members of the Group included Margaretha Granborg, Senior Administrative Officer, Ministry of Industry and Trade; Hans Hellström, Research Associate and Tommy Söderström, Chief Consulting Physician representing the Federation of Swedish County Councils and the county councils; Anders Lindgren, Deputy Director, Ministry of Health and Social Affairs; Ingvar Sjöholm, Professor, Medical Products Agency; Bengt Wadman, Medical Adviser, National Swedish Board of Health and Welfare; Professor Britta Wahren, Swedish Institute for Infectious Disease Control; Olof Åkerblom, Associate Professor, Swedish Society of Medicine; and Benny Åsberg, Chairman, Swedish Hemophilia Society. This document was originally published in Swedish and later translated into English by Ron Gustafson.

1.1 Problem Description

In Sweden, blood plasma collection is a responsibility of the health services. Hence, the medical authorities (county councils) are primarily responsible for ongoing plasma activities. There are, however, no regulations requiring the county councils to collect blood plasma which will not be used for direct transfusion to

patients, but which instead is sold to the fractionation industry to manufacture drugs.

In 1985, the government commissioned the National Swedish Board of Health and Welfare to monitor the progress toward self-sufficiency in blood and blood plasma as presented in the 1975 recommendations by the World Health Organization.(2) Swedish progress toward self-sufficiency has been described in a report from the Federation of Swedish County Councils and in annual reports from the National Swedish Board of Health and Welfare in collaboration with the Swedish Association for Transfusion Medicine.(3,4) According to current international criteria, Sweden achieved the goal of self-sufficiency in the early 1990s.

The European countries are basically self-sufficient in erythrocytes, platelets, and plasma used for transfusion. On the other hand, Europe is dependent on the import of source plasma for manufacture of plasma drugs.(5) These drugs are essential for certain groups, e.g. patients with hemophilia or certain immune deficiency diseases.

The problem which created the need for the Working Group is that Swedish and European plasma collection activities are having difficulty competing with corresponding U.S. activities in terms of the price of source plasma. Part of the explanation for the lower prices in the United States is that the regulations concerning plasma collection volumes and collection intervals are different in the U.S. and Europe. For the past few years, there has been a risk that Swedish plasma donation activities must be discontinued due to the competition presented by cheaper U.S. source plasma.(6) Ongoing reorganizations of the international plasma industry have made the problem seem more acute during the past year.(7,8,9)

Discontinuation of existing plasma activities would be a serious threat against Swedish and European self-sufficiency in plasma and plasma products. The goal of self-sufficiency in blood and blood products within the EU by voluntary, unpaid donation was established by a EC directive in 1989 and has been addressed, e.g. in the resolution in the Council of the European Union from November 12 1996.(10,11) In the resolution, also supported by

Sweden, the member states are instructed to review elements in their policies, procedures, and programs which aim to guarantee safety in the blood transfusion chain and in self-sufficiency of blood.

1.2 The Charge

The Working Group was charged with designing a long-term strategy to address how Sweden can meet the demands on safety in blood transfusion and blood self-sufficiency. The Group was asked to design its work according to the EU resolution of November 1996. To achieve a long-term solution to the problem, the government believes that Sweden should act in collaboration with the rest of Europe, primarily with other EU countries.

The charge to the Working Group was to:

1. investigate how safety demands in Sweden can be harmonized with EU directives and guidelines;
2. review the cost of plasma donation in light of given safety standards;
3. identify price and competitive conditions related to Swedish plasma supply; and
4. identify other circumstances significant to Swedish plasma supply.

1.3 Implementation

The Working Group met for the first time on March 4, 1997. Thereafter, thirteen meetings were held, including two hearings with representatives of the Association of the Swedish Pharmaceutical Industry, and one hearing with representatives from Swedish blood and plasma banks.

To acquire an evidence base, obtain opinions, and anchor the work of the Group, many contacts were made with representatives of the medical sector and industry. Data on costs for source plasma,

prices, and competitive conditions were compiled, partly with the help of two questionnaires designed for the blood and plasma banks in Sweden. Michael Högberg from Spri was responsible for collecting and analyzing the economic data.

To obtain an understanding of ongoing work and planned initiatives within the EU, representatives of the Working Group visited the DGV of the European Commission in Luxembourg, which is responsible for questions regarding plasma for transfusion and European self-sufficiency. The DGIII in Brussels, which is responsible for pharmaceutical-industrial issues, e.g. issues concerning plasma for fractionation, was also contacted for information exchange. At a meeting in the Dutch Health Ministry in the spring of 1997, representatives for the Swedish Working Group and members of the equivalent Dutch working group, informed each other of their views and plans. Contacts were also made with other EU countries, mainly France, Germany, and Austria.

A practical goal concerning the work of the Group was to develop a base of evidence for the government prior to the EU Council of Health Ministers on June 5, 1997. The recommendations of the Group are presented in a special background document (Appendix 1). Two problems were emphasized in the document: differences in regulations and recommendations concerning plasma collection routines between Europe and the United States, and their negative influence on European competitiveness in plasma activities; and the lack of scientific evidence on the optimal use of plasma and plasma products. The responses to the Swedish document were generally positive. At the end of June 1997, the mandate of the Working Group was extended by the government with the aim to support and follow up the initiatives introduced in the document.

In the beginning of November 1997, a meeting for national experts in the self-sufficiency issue was arranged by the European Commission DGV, which offered the Working Group another occasion, in a Euopean forum, to express their opinions on the measures needed to promote European self-sufficiency (Appendix 2). Shortly thereafter, the European Commission announced its suggestion for recommendations to the Council on the suitability of

blood and plasma donors and screening of donated blood. This was presented at the Council of Health Ministers' meeting in Luxembourg on December 4, 1997. Recommendations concerning higher maximum plasma collection volumes per session than previously recommended by the Council of Europe were included. The Working Group has expressed its opinions and comments to the suggestion of the Commission on repeated occasions. At the council of Health Ministers meeting in Luxembourg on April 30 1998, the Council arrived at a political agreement on the recommendations in a revised form (Appendix 3).

During the spring of 1998, the initiation of an international study of plasma collection volumes was discussed with representatives of the European Commission, the German and Austrian Council of Health Ministers, and the French Blood Institute. The Swedish Medical Research Council has been involved in the planning of research activities in the plasma field.

2 Goal of Self-Sufficiency

2.1 Blood Plasma and Plasma Proteins

A human adult has between four and six liters of blood. Approximately half of the blood volume consists of a transparent fluid, plasma, containing protein and salt. The remaining blood volume consists of different types of blood cells: red blood cells (erythrocytes) which transport oxygen to the tissues, white blood cells (leucocytes, lymphocytes) which are involved in the infection and immune defense of the body, and blood platelets (thrombocytes) which contribute to blood coagulation.(13)

Blood plasma contains a number of proteins which are essential to the human body. Among the most important are immunoglobulins, i.e. antibodies against various microbes which, for example, have developed from previous infections or as a result of vaccination. Other important proteins include the coagulation factors required for the blood to coagulate after injuries and bleeding, and albumin, which contributes to maintaining pressure in the blood vessels and transporting various substances through the body.

Some plasma proteins may be lacking or insufficient in certain congenital diseases. In hemophilia, the patient lacks of one of the coagulation factors and has an increased tendency to bleed.(14) Hemophilia exists in two main forms; hemophilia A, which is due to a lack of coagulation factor VIII, and hemophilia B, which is associated with a lack of factor IX. Approximately 80% of the 600 to 700 Swedish hemophilia patients suffer from hemophilia A and 20% suffer from hemophilia B. Treatment basically involves injecting or infusing the missing factor. Another congenital bleeding

disorder, which may require treatment with special plasma products, is von Willebrand's disease.

In some primary immune deficiency disorders, the patient lacks the ability to produce certain immunoglobulins.(15) The most benign type, a lack of immunoglobulin A, affects approximately 1 in 500 Swedes, but usually causes few symptoms. The other primary immune deficiency diseases are rare, but several are so serious that the patient's life depends entirely on the continuous administration of immunoglobulins.

Apart from congenital diseases, individuals with some other conditions may also require administration of plasma proteins. In patients with burn injuries, large amounts of body fluid are lost, including albumin, which must be replaced. In cases of severe bleeding, patients may be treated with various blood components. To prevent contagious diseases, individuals traveling to countries with severe epidemics are commonly given antibodies extracted from plasma, i.e. gamma globulin. Gamma globulin can also be used for prophylaxis of infection in patients with decreased immune defense related to malignant diseases. Patients with infections such as unconfirmed blood poisoning or certain neurological diseases may benefit from gamma globulin treatment.

2.2 Industrial Production of Plasma Products

Plasma proteins, which have been purified and concentrated (through an industrial process) for medical use are called plasma products. The manufacture of plasma products – plasma fractionation – is based on plasma collected in two alternative ways; the source plasma fractionated is either recovered plasma or source plasma.

Some countries rely mainly on recovered plasma. This is obtained as a byproduct from collecting whole blood. The supply of recovered plasma is dependent on how the blood establishments use blood cells and how medical services are organized. In several

European countries, e.g. the Netherlands and Finland, non-commercial national plasma fractionaters have a predominant position, and use largely recovered plasma.

Since the demand for plasma products has been gradually increasing, and in many countries has reached levels which cannot be fully met by recovered plasma, much of the plasma supply is now based on plasmapheresis. Through this procedure only the plasma is collected and the blood cells remain in the donor. Blood donors lose part of the oxygen-carrying capacity of the blood, which is restored relatively slowly. Plasma donors only lose the proteins in plasma and retain their capacity for oxygen transport. Since plasma proteins are reproduced more rapidly than blood cells, it is possible to collect a larger volume each time and collect from a donor more often.

In most cases, blood establishments have acquired plasmapheresis equipment and deliver source plasma directly to fractionaters. In Sweden, plasma fractionation is done by the private plasma industry, which uses mainly source plasma (over 60%).

The most important plasma products manufactured and marketed today are:

Coagulation factors

1) Factor VIII; marketed in Sweden under the name Beriate (Hoechst), Haemate (Hoechst), Hemofil M (Baxter), Immunate (Immuno), Monoclate P (Urgentum), and Octonativ M (Pharmacia & Upjohn).
2) Factor IX; marketed in Sweden under the name Immunine (Immuno), Mononine (Urgentum), and Nanotiv (Pharmacia & Upjohn).

Immunoglobulins

1) For intramuscular or subcutaneous injection; Beriglobin (Hoechst), Gammaglobulin and Gammanorm (Pharmacia & Upjohn), Immunglobulin (Immuno).

2) For intravenous use; Endobulin (Immuno), Gammagard S/D (Baxter), Gammonativ (Pharmacia & Upjohn), Nordimmun (Novo Nordisk), Octagam (Octapharma), Polyglobin (Bayer), Sandoglobulin (Sandoz).
3) Specific immunoglobulins are manufactured and marketed for Rh-immunization, tetanus, chicken-pox/shingles, hepatitis B and cytomegalovirus by SBL, Centeon, Hoechst, Pharmacia & Upjohn, and Lövens.

Albumin
Marketed as a plasma substitute by Bayer, Baxter, Behring, Immuno, Novo Nordisk, Pharmacia & Upjohn, and Urgentum. Furthermore, it has a wide field of application as a stabilizer, e.g. in various vaccines.

2.3 The Term ”Self-sufficiency”

In the light of the fact that many end products can be extracted from source plasma, it is not evident on which grounds and by which criteria the degree of self-sufficiency in blood plasma should be defined. Several of the end products mentioned, in practice mainly factor VIII, can also be manufactured by an alternative, recombinant process, which complicates the issue.

On a national level, it has been common to relate the volume of source plasma produced in a country to the national use of plasma products. The level of self-sufficiency is then defined in view of the end product requiring the largest volume of source plasma needed for the collection volume to correspond to national consumption.

The term ”community self-sufficiency” is used within EU to imply the state of self-sufficiency within the European Union as a geographic whole.[5] According to this approach, self-sufficiency at a Union level can include a situation where some member states have a shortage of plasma that can be offset by a surplus in other member states. Some EU countries that basically support the idea of European self-sufficiency have, however, had difficulties app-

lying this approach in practice. Although the primary issue for EU is that of self-sufficiency on a European level, national self-sufficiency has been viewed as a strategically important step toward the European goal.(16)

For several years, the product which was considered to be a standard in plasma collection has been coagulation factor VIII for the treatment of hemophiliacs. Since a transition is starting to take place from plasma derived factor VIII to a corresponding recombinant product, the consumption of albumin is now referred to as a baseline in plasma collection. Nevertheless, many believe that the need for, and potential applications of, various types of immunoglobulins will drive the future demand for plasma used in fractionation.

Essentially, the term self-sufficiency refers to the balance between supply and demand.(17) The *supply* of plasma depends largely on the number of recruited donors, their motivation, and how often they are willing to give plasma. The amount of plasma collected also depends on the number and volume of plasma units collected. The *demand* for plasma is associated with the occurrence of certain diseases, e.g. hemophilia, in the population. Besides epidemiological need, demand is also influenced by several other factors, such as industrial exchange of factor VIII from source plasma. The degree of exchange is related to the virus inactivation processes applied in association with plasma fractionation. If the exchange is high (e.g. around 25% instead of 20%), a somewhat smaller amount of source plasma is required for the manufacture of the same amount of factor VIII.

In 1996, 256 000 kg of plasma was produced for fractionation in Sweden, of which 57% (nearly 147 000 kg) was collected via plasma donation (source plasma) and the rest from collecting whole blood (recovered plasma).(18) The amount of plasma for fractionation exceeded, for the first time, the Swedish demand for factor VIII, which according to estimates by the National Swedish Board of Health and Welfare corresponds to between 185 000 kg and 213 000 kg of source plasma. Within EU as a whole, however, there is a severe shortage of plasma. In 1993, the amount of

collected plasma for fractionation was – according to the Commission's calculations – approximately 3 720 000 kg, while the need was estimated at between 5 110 000 kg and 6 140 000 kg, depending on the industrial exchange level.(5)

In this context, it is important to remember that the demand for various plasma products is ruled largely by current clinical practices, treatment indications, and the prevailing traditions in different countries. In this respect, major variations in practice have been found among the European countries.(19) There are also regional variations within Sweden in the use of plasma products.(20)

Disagreement about optimum strategies for treating the various conditions where plasma products can be used makes it difficult to reasonably estimate the current and future demand for these products. Hence, the demand for source plasma cannot be calculated or clearly predicted. Obviously, this creates a major obstacle when estimating self-sufficiency levels.

2.4 Statements by WHO, the Red Cross, and the Council of Europe

In 1975, the 28th General Assembly of WHO recommended that member nations organize blood donation on a voluntary basis and without financial compensation.(2) The member nations were also instructed to take legal and other actions to protect and promote the health of both blood donors and recipients. The document also mentioned that commercial plasma donation could threaten the organization of national blood services based on unpaid donors. The recommendation from WHO was followed by similar resolutions from the International Red Cross and the International Society of Blood Transfusion, ISBT.(21,22)

Common to these decisions is the fact that commercial donation was viewed as a potential problem, both in terms of infection and in terms of the safety of donors. Paid donation was considered to attract donors having a poor socioeconomic and health status, and hence increase the risk for carriers of infection. Furthermore, paid

donation might lead to more frequent donations, causing a deterioration in the health of donors. Given this background, it was also desirable to emphasize the ethical implications of commercial plasmapheresis. The increased commercialization of blood collection and plasmapheresis, which has occurred particularly in the developing countries, has also been observed in Sweden.(23)

In Europe during the 1980s, the various decision-making authorities of the Council of Europe expressed their support for the goal of national self-sufficiency in blood and blood products by voluntary, unpaid donation.(24,25) In the recommendation of the Council of Europe from March 29, 1990, collaboration in this respect is also encouraged among the different member countries of the Council.(26)

While WHO has been working globally to ensure quality and safety in blood and plasma activities the Council of Europe has, for several decades, performed extensive work to create common European guidelines and standards in the field. Safety issues related to blood products and regulations and guidelines designed by different national and international organizations in these issues are described further in Chapter 3.

2.5 EU Directives and Resolutions

Within the European Union, the goal concerning self-sufficiency in blood and blood products by unpaid donation was introduced for the first time in a EC directive from June 14, 1989.(10) For Sweden, the directive became binding with entry into EU. The goal concerning self-sufficiency is clearly presented in Article 3, Paragraph 4, of the directive:

> *Member States shall take the necessary measures to promote Community self-sufficiency in human blood or human plasma. For this purpose, they shall encourage the voluntary unpaid donation of blood and plasma and shall take the necessary measures to develop the production and use of products*

> *derived from human blood or human plasma coming from voluntary unpaid donations. They shall notify the Commission of such measures.*

Self-sufficiency within the EU is, in principle, facilitated by the free mobility of goods across the internal market since blood and blood products from a member country having an excess supply can be freely sold and used in another member nation. A necessary condition is, however, that the states can rely on the safety regulations and routines applied in blood and plasma activities in other states. Hence, there is a clear link between the European work for increased harmonization concerning blood safety and the desire for self-sufficiency in blood products within the Union.

Since 1989, the European goal has been confirmed and amended in several position papers from the European Council of Health Ministers; in the decision of a European program to combat AIDS (June 1991), in conclusions concerning self-sufficiency of blood (December 1993), and in the resolution concerning safety and self-sufficiency of blood (June 1995).(27,28,29) The European Parliament accepted four resolutions having a similar thrust from 1993 to 1996.(30,31,32,33)

The Council resolution for a strategy concerning safety in blood transfusions and blood self-sufficiency in the European Union dates from the Council of Health Ministers' meeting on November 12, 1996.(11) It is based largely on conclusions and recommendations from an expert symposium in Adare, which emphasizes that blood self-sufficiency in the Union must adhere to the principle that blood donations shall be voluntary and that donors will not be remunerated.(11,34)

Two principle recommendations are made by the Council. One is aimed at the member states and the other at the European Commission. The member states are encouraged to review the elements in their policies, procedures, and programs which are intended to guarantee safety in the blood transfusion chain according to the conclusions and recommendations from the Adare symposium. The Commission is recommended to quickly make suggestions

supporting the actions of the member states, for the purpose of promoting the development of a coordinated strategy for the safety of blood and blood products.

Since the late 1980s, the European Commission has actively followed up on the collection and use of blood, plasma, and plasma products in the member nations. Together with the Council of Europe, a first report of the situation was published in 1989 and further reports were published in 1991 and 1993.(35,36,5) In the progress report concerning the situation in 1993 it was noted that, while the EU was then nearly self-sufficient in blood and blood components, the shortage of plasma within the Union had grown and import of plasma and plasma products was still required.

The negative trend in the self-sufficiency situation and the delay by the European Commission in suggesting and taking action in the field have been subjected to criticism from some member states. The Netherlands, which held the Chair of the European Union during the first half of 1997, presented (on June 5, 1997) a basis for discussion calling for concrete priorities and speedy action, particularly concerning greater blood safety.(37) Sweden basically supported the Dutch initiatives and suggested additional actions, e.g. to increase the competitiveness of European plasma (Appendix 1).

During the autumn of 1997, the EU work was managed by Luxembourg, which at the meeting of the Council of Health Ministers in June, explained that blood issues would continue to have a high priority. In December 1997, the Commission presented a suggestion to amend Council recommendations concerning screening and testing of blood and plasma donors, including new recommendations concerning allowed collection volumes. At the meeting of the Council of Health Ministers in Luxembourg on April 30, 1998, the Council approved the contents of the recommendations in revised form (Appendix 3).

Representatives of DGV have stated that it is the Commission's intention to support European research on alternative plasma collection schedules – a study with participants from Sweden, Germany, and Austria. Furthermore, the Commission is continuing to

plan activities in the blood field, e.g. guidelines for inspections and quality assurance of blood and plasma products.

2.6 Concluding Remarks

By definition, the term ”self-sufficiency” concerns the balance between supply and demand. The supply of blood plasma depends on access to donors and the number of collected plasma units and their volume. Demand for the end products manufactured from blood plasma is linked to the occurrence of certain diseases in the population. It is, however, important to note that demand is also guided by prevailing clinical practice, i.e. the prevailing treatment traditions in different countries. Major variations in this respect have been found among the European countries and among different areas in Sweden. These factors present a significant problem when assessing the self-sufficiency situation.

As early as 1975, WHO decided to encourage the member nations to organize blood donation on a voluntary non-remunerated basis. The background to the suggestion was the increased commercialization of blood collection and plasmapheresis, particularly that which has occurred in the developing countries. This was viewed as a potential problem, from the perspective of infection and the perspective of donor safety. The ethical implications of commercial plasmapheresis were also emphasized since socieconomically disadvantaged groups might be encouraged to donate blood and plasma more frequently.

Since the issue was considered to have an ethical dimension, the various decision-making assemblies of the Council of Europe, during the 1980s, expressed their support for the goal of national self-sufficiency in blood and blood products by voluntary, unpaid donation. In 1990, the Council of Europe encouraged its member states to collaborate in this area.

Within the European Union, the goal of self-sufficiency in blood and blood products by unpaid donation was introduced in an EC directive from 1989. The directive was based in part on earlier

decisions by the Council of Europe, but can also be seen as a part of EU's effort to harmonize regulations aimed at promoting the free mobility of goods on the internal market. The term "community self-sufficiency" as it is used within EU implies self-sufficiency within the European Union as a geographic entity. Although the primary issue for EU is to become self-sufficient on a European level, national self-sufficiency has been viewed as a strategically important step toward achieving the European goal.

3 Safety Issues Related to Blood Products

Historical experience has taught us that several known and unknown infectious agents, especially viruses, can be transmitted from donor to recipient via plasma and plasma products. The unforeseen spread of HIV/AIDS during the 1980s brought extensive human suffering and caused political turbulence in many countries. It cannot be ignored that we may face similar problems in the future, caused by unknown viruses or other contagious agents. Given the free mobility of blood products within EU, it is necessary to aim for a common, harmonized approach toward uniform safety standards in the European Union. The conditions, however, are far from uniform, even though the regulatory processes for approval and control of plasma products are supposedly the same throughout EU. There are historical factors underlying this situation.

In most member states, activities concerning the use of different blood components for transfusion purposes has been considered part of the nationally regulated medical services. Plasma pharmaceuticals were handled nationally in several of the member states until 1992, and the different national plasma fractionating companies had a very strong monopoly-like position in their respective home countries. The situation concerning blood components for transfusion purposes is still under strict national control, while plasma derivatives of European origin should follow the regulations established by EU. However, certain national requirements may still play a role in some of the member states.

This report presents the supranational regulations that apply within EU regarding plasma for fractionation and for plasma

derivatives approved as drugs. To some extent, the same safety requirements also apply for plasma and blood intended for transfusion, since it is not always known beforehand whether a donation will be used for industrial fractionation or be directly transfused to a patient. In reality, this means that some tests and standards needed for transfusion products would not have been required to guarantee safety in plasma for fractionation. Toward the end of the chapter, the most important national directives concerning quality and safety of plasma activities are summarized. Appendix 3 presents the recommendations on which EU health ministers recently reached political agreement concerning the suitability of blood and plasma donors and screening of donated blood.

3.1 On Blood Contagion

During the acute phase of an infection, contagious agents may appear in the blood. This phase is usually associated with clinical symptoms such as fever, which are easily observed. Certain infectious agents, such as HIV and hepatitis C virus, may be present in a latent or chronic phase, without clear symptoms. Each year, researchers discover new infectious agents, and some of these may have adverse consequences if they infect the recipient of blood or blood products. In particular, infectious agents which reside in blood cells or which reach the blood through constant or acute secretion create a problem in the transfer of blood or tissues between individuals.

Products manufactured from blood and blood plasma have reached a level of sophistication which makes it possible to separate out pathogens that cause acute infection, with the possible exception of long-term consequences from the transfer of genetic material or certain proteins.(38)

The blood-borne infectious agents for which all blood is tested are HIV-1 and HIV-2, hepatitis B virus (HBV), and hepatitis C virus (HCV). Different countries test, to varying extents, for other

infectious agents, e.g. human T lymphotropic virus (HTLV) I and II and syphilis spirochetes. Some test at each donation, others only test new donors, and some do not test at all. The HBV test looks for the antigen, while the other tests look for the presence of antibodies. There is a very low risk that blood or plasma donors are in the incubation stage of an infection and that antibodies have not yet been formed. The infectious agent can then possibly be determined by an antigen test or by testing for its nucleic acid. In the manufacture of plasma products, possible infectious agents are separated or inactivated. Starting in 1999, the testing for HCV will be completed by nucleic acid test (NAT) on pools of source plasma. Such testing is likely to be extended to include the nucleic acids of other viruses.

Bacteria occur in plasma during the acute phase of certain infections. They are inactivated during the production of plasma products.

Recently identified blood-borne agents where the disease is mild or unknown, are B19 parvovirus, hepatitis G virus, and herpes virus type 8. Since these infectious agents occur frequently, they cannot be isolated through selective collection of blood and plasma or through anamnestic data from donors. Nearly all plasma pools, contain, e.g. hepatitis G virus before virus inactivation. The adequate approach is treatment of, or testing for, the organism.(39,40,41,42)

Prion disease, such as the new type of Creutzfeldt Jacob disease related to mad cow disease, may possibly be transmitted via blood. Anamnesis can be used to exclude unsuitable donors. Prions in blood and plasma cannot be inactivated by chemical or physical treatment.(43)

3.2 Regulatory Principles to Optimize Plasma Safety

Because the industrial development of large-scale plasma fractionation makes it possible for a donation, which is a small part of a large plasma pool, to infect a large number of patients via various fractionated plasma products, there are potentially large risks associated with the use of plasma as a primary pharmaceutical product. Consequently, finely detailed guidelines have been designed over the years, and requirements and tests have been implemented during different phases of plasma collection and fractionation. The following control principles and steps in plasma management can be identified:

3.2.1 Selection of Suitable Donors

Obviously, the primary goal is to attempt to avoid contamination in the initial material (blood or blood plasma) by some known infectious agent. As mentioned above, the regulations for collection of plasma/blood originally developed on a national level and were determined by the need for safety in transfusion. At an international level, WHO used national experts to develop recommendations on the reliable selection of suitable donors. These are presented in the WHO report *Requirements for the Collection, Processing, and Quality Control of Blood, Blood Components, and Plasma Derivatives* from 1994.(44) The guidelines were mainly designed to meet the needs in developing countries and are to be viewed as basic standards. Therefore, the WHO guidelines have not been fully implemented in EU member states and other industrialized countries.

The countries in Europe have consolidated their expertise in the transfusion field within the Council of Europe's Public Health Committee and its guidelines group on Blood Transfusion and Immunohaematology, which published their recommendations in the *Guide to the Preparation, Use, and Quality Assurance of Blood*

Components. This was published in its 4th revised edition in 1998 as a supplement to the European Council *Recommendation No. R (95)15*. (45) Technically, these regulations have the character of guidelines, and hence the member states are not required to implement them via national legislation.

An attempt to make the recommendations binding was made during the summer/autumn of 1996 within the European Pharmacopoeia collaboration in association with the revision of monograph 1997:0853, *Human Plasma for Fractionation*.(46) However, the attempt failed since some member states used their veto right, and the monograph, therefore, only refers to the European Council recommendation concerning the selection of donors.

The European Council guidelines have the dual purpose to ensure that a donation is of acceptable quality and does not contain hazardous agents, and to protect the donors against a dangerous loss of blood or plasma. As previously described, plasma for fractionation can be obtained from whole blood or in plasmapheresis. The requirements to be fulfilled in these donations are described in two separate sections. Donors shall have good health. This is checked by anamnesis (questionnaire on health shall be filled out) and routine tests. When required, the data shall be completed by further questions and examinations.

Furthermore, the guidelines specify the volumes which can be donated on each occasion and how often the donor can give blood or plasma. Six hundred and fifty ml is the recommended maximum volume for plasma collection in one session, including anticoagulant solution. According to the guidelines, plasma collection should not take place more often than every second week. No more than 15 liters of plasma per year should be collected from an individual donor.

The new EU recommendations differ somewhat from the guidelines from the Council of Europe. According to EU, the maximum volume per collection is also 650 ml, but anticoagulant is not included in this volume. There is no annual maximum volume in the EU recommendation. Rather, it emphasizes the lack of scientific knowledge and the need for research in the field.

3.2.2 Control of Individual Donations

Exams and the information from donor questionnaires is evidently insufficient to guarantee safety in either transfusion activities or in plasma derivatives. National guidelines also require testing of the individual donations to reasonably guarantee safety in transfused blood components. These requirements may differ from country to country, but all countries have established requirements in testing for hepatitis B and for antibodies of HIV and hepatitis C.(47)

In regard to plasma or other blood components used in industrial production, there are guidelines issued by the central authority for pharmaceutical approval within EU, the European Agency for the Evaluation of Medicinal Products, EMEA, and its group of experts, the Committee for Proprietary Medicinal Products, CPMP. The latest revision of these guidelines, *Note for Guidance on Plasma Derived Medicinal Products,* involves an update of the control of virus safety in plasma, which is used in the manufacture of plasma proteins.(48) These guidelines also refer to the Council of Europe recommendations and to the European Pharmacopoeia monograph. The Pharmacopoeia requirements of testing are further described below.

3.2.3 Inactivation of Contaminated Virus in Plasma for Fractionation

The guidelines given above from the CPMP also specify that each manufacturing process shall include fractionation steps, which have the capacity to inactivate or separate viruses that could possibly contaminate the source plasma. The reason for this requirement is that no method currently available can guarantee a total absence of virus or virus antigens. Furthermore, antibody tests are the only tests available for some viruses (which indirectly detect an infection, but not a virus).

The inactivation processes used in the fractionation of plasma can be based on different principles. Chemical treatment methods seem to be the most effective. TNBP (tri-nitro-butyl-phosphate)

can, e.g. along with a suitable detergent ("the solvent-detergent-method") effectively inactivate envelope viruses containing lipids. Alcohol also inactivates certain viruses. Heat, e.g. pasteurization (60°C, 10 hours), is considered to be an effective way to inactivate hepatitis B in albumin. In some cases, chromatographic separation methods can be very effective. Lately, even physical methods have been applied, e.g. nanofilters which do not allow passage of larger virus particles.

The guidelines also stipulate that the different steps of the fractionation process should be validated in terms of their capacity to inactivate viruses. Validation can be done by using different model viruses representing different groups of virus (DNA or RNA viruses, small or large, encapsulated or unencapsulated, heat-resistant viruses), and should confirm that the probability for virus remaining in the processed specimens is very small.

3.2.4 GMP, Compliance Control, and Batch Release

The regulations for manufacturing plasma-derived products are extremely strict as regards the application of Good Manufacturing Practices, GMP. All steps in production must be validated and strictly followed. Changes in the production process must be approved by the authorities after assessing the validation data from the manufacturer. There are only limited possibilities to retrospectively check compliance with GMP in all steps of the production (including plasma collection) but some retrospective control is maintained through inspections and laboratory analysis of source plasma and end products.

The Pharmacopoeia monograph states that prior to start of a fractionation process, the manufacturer shall recheck for any possible virus contamination in smaller pools of the plasma obtained. The virus tests prescribed for each individual donation shall then be repeated using a reagent of the most recent generation. Similar regulations apply according to the CPMP guidelines. In addition,

these include requirements for official control by virtue of a so-called batch-release process. According to these guidelines, the authorities shall perform a protein chemical analysis on the end product using a predetermined program for each product, and plasma batches are tested using routine virus tests. This type of batch-release control is being implemented in EU, and shall be done once on each batch manufactured within the union. Each manufactured batch shall be accompanied by a certificate issued by the controlling authority so that it does not have to be rechecked by another member state.

As mentioned above, the virus tests currently available are not absolutely reliable. Furthermore, antibody tests have a ” window”, within which a recently infected donor of plasma or blood has not yet developed detectable levels of antibodies. This window may remain open for up to half a year in HCV or HIV infections, but the introduction of new tests may cause the window to gradually become smaller. Development work is being carried out by EU in collaboration with other regulatory bodies and WHO to investigate the possibilities to introduce standardized methods to discover virus genomes by means of various gene amplification methods, e.g. by NAT(PCR)-based methods. Recently, decisions have been made within EU to start testing for HCV in pools of plasma for fractionation, beginning July 1, 1999.(49)

3.3 Controls for Virus and Prions

The Pharmacopoeia monograph on plasma for fractionation specifies the compulsory virus tests which should be performed on each donation and on the in-process checks of plasma pools. The CPMP guidelines also refer to the Pharmacopoeia concerning testing. There is full agreement that tests should be performed on hepatitis B virus (HBV, HBsAg) and on the antibodies of HIV-1, HIV-2, and HCV. Testing for anti-HIV-1 and anti-HIV-2 normally involves using the same testing kit. Apart from the tests mentioned, the authorities can also require testing for the enzyme alanine-lysine-aminotransferase

(ALT) ”while waiting for complete harmonization” according to the Pharmacopoeia. Elevated *ALT*-levels may indicate liver involvement, which may be caused by a viral infection. Opinions concerning the test are divided. Most claim that it does not enhance safety due to wide variations, even in healthy individuals, and keeps 1% to 2% of the donations from being used for no real reason. Others claim that the test provides an early signal of hepatitis and even information on viral infections, for which we cannot yet test. The requirement to test for ALT as specified in the Pharmacopoeia is a compromise, and it is likely that the test can be discontinued within a few years.

The test of *HBsAg* is a sensitive and direct method of testing for virus antigen. There appears to be agreement that plasma derivatives do not transmit HBV if one considers the processes that separate and kill viruses during plasma fractionation.

The *HIV* and *HCV* tests are based on testing for the presence of antibodies. To achieve acceptable safety in plasma products, the fractionation process must include adequate and validated inactivation and/or separation methods for the respective viruses. The solvent-detergent-method is considered to offer adequate safety in this respect. Prior to the application of this method, there was substantial hesitance to use the anti-HCV test, as it was considered to exclude donations with high levels of ”good”, protective antibodies. In a plasma pool, the antibodies were believed to neutralize any excess HCV which might possibly accompany some donations.

Generally, earlier criticism against the anti-HCV test is probably relevant, and it has attracted renewed interest in discussions concerning testing for other viruses, e.g. *hepatitis A virus* and *parvovirus B 19*, which are not inactivated by the solvent-detergent-method. During the past 5 years, several cases of HAV transfer via blood products have occurred due to failure to comply with GMP, but it is uncertain whether testing can be viewed as a cost-effective strategy. An alternative would be to require a minimal level of anti-HAV in plasma pools as protection against contamination. The presence of parvovirus B 19 and its significance for the recipient’s health has yet to be clarified.

A special case in assessing the safety of blood products concerns the potential transfer of the *BSE-prion*. Previous scientific investigations have been unable to demonstrate that BSE is transmitted via plasma-derived products, except when implanted directly into the brains of test animals. The recently reported cases from England of the so-called new variant of Creutzfeldt-Jacob disease (nvCJD), however, throws a shadow of uncertainty on previous conclusions. The Council of Europe recommends that persons with Creutzfeldt-Jacob disease, or with the disease in the family, shall not be permitted to donate blood or plasma. The EMEA has, as a measure of safety, decided to withdraw drugs containing plasma from donors who later developed nvCJD.(50,51) In November 1997, in Sweden and several other European countries, two batches of a radiopharmaceutical used to diagnose blood clots in the lungs were withdrawn. The reason was that the batches contained human albumin, and that one of the donors whose blood was used to manufacture the batch had later died from nvCJD.(52)

3.4 Domestic Regulation

At a national level, the blood establishments in Sweden are supervised by the National Swedish Board of Health and Welfare and the Medical Products Agency. The authority of the Medical Products Agency includes inspection of the blood establishments that produce blood components that are used as raw material in the manufacturing of drugs and plasma. The authority of the National Swedish Board of Health and Welfare covers the blood components used directly by patients. The National Board has made its regional unit in Örebro responsible for the national coordination of blood-related issues.

The National Swedish Board of Health and Welfare has also issued several directives and recommendations aimed at regulating quality and safety in blood and plasma activities. To some extent, the issue of self-sufficiency is also addressed. In their *General Advisory on Blood Operations* from 1984, the National Swedish

Board of Health and Welfare emphasized that it agreed with WHO's recommendation to member states to become self-sufficient in all products manufactured from human blood.(53) New discoveries concerning the manufacture and use of blood and blood components were described against the background that whole blood for transfusion was being increasingly replaced by more differentiated and specific treatment using various blood components.

The document emphasized that greater collaboration within and among the healthcare regions was necessary to meet the total need of blood and blood products in the country, and to obtain a sufficient volume of source plasma for industrially fractionated products. The existing organization of blood establishments was considered to work well and no changes were proposed. Hence, the structure comprised of type I and II blood establishments was maintained. Type I blood establishments are found in regional hospitals and meet the needs for diagnostic and therapeutic services at the regional hospital. They also provide necessary consultant services to the county and the county district hospitals within the region. Type II blood establishments are found in county hospitals and in most county district hospitals. They meet the needs of diagnostic and therapeutic services at this level of care.

The *National Swedish Board of Health and Welfare Regulations on Blood Donation, Blood Transfusion etc* from 1989 presented e.g. the criteria for assessing the suitability of blood donors, considering risks to both the donor and the recipient of blood and blood components.(54) The document stipulated that in hemapheresis, which involves separation of plasma, a maximum of 15 liters of plasma (anticoagulant excluded) could be collected per year, and a maximum of 550 ml of plasma could be collected per session. For blood donors weighing more than 80 kg, the latter volume could be increased to 600 ml. Hence, the current Swedish directives are comparable to the recommendations issued by the Council of Europe. However, the limits are more restrictive – both concerning the maximum allowed volume per collection and the

total annual volume – than the EU recommendations presented in Appendix 3.

In assessing the suitability of blood donors, considering the risk for the spread of viral infection to the recipient, actions to prevent the spread of hepatitis B and hepatitis-non-A, non-B-virus, and HIV were presented in the National Swedish Board of Health and Welfare procedures. Actions to prevent the spread of malaria and other non-domestic epidemic diseases were also described. The problems of HIV/AIDS had already been addressed in a previous document from 1985.(55) The regulations concerning viral contagion have since been completed as regards examination of donors for *hepatitis C virus* and *HTLV I/II*.(56,57) Generally, the Swedish regulations are considered to be in harmony with the European regulations.

In the light of the increased attention to the risks involved to the recipient during administration of blood products, such as albumin and plasma, the National Swedish Board of Health and Welfare in 1991 issued a *General Advisory on Replacing Blood Loss*.(58) An essential consideration was that blood products should be used only on strict medical indications and after careful consideration of the documented characteristics and qualities of the blood components in question. According to the guidelines, mainly artificial crystalloids and colloids or albumin should be used in treating blood loss. Plasma should be used only in cases where a need exists for coagulation factors or their inhibitors, and not solely on the indication of volume expansion. This guidelines may have contributed toward reducing the indiscriminate use of albumin and plasma by the health services.

The Medical Products Agency is the authority responsible for overseeing compliance with the *Pharmaceuticals Act (1992:859)* and the regulations and conditions addressed in the legislation. According to the Pharmaceuticals Act, blood components used as raw materials in the manufacture of drugs are referred to as pharmaceuticals. Collection of blood or plasma intended for the manufacture of drugs, is part of the manufacturing process, and

should be carried out in accordance with current good manufacturing practices, GMP.

The Medical Products Agency inspects blood establishments that manufacture blood components to ensure that manufacture and control take place according to GMP, which is a prerequisite for a manufacturing license to be issued according to the instructions of the Medical Products Agency.(59) Blood establishments are required to have such a license from the Medical Products Agency to be permitted to deliver blood components to companies that manufacture pharmaceuticals.

The Medical Products Agency had previously issued *Directives for Good Manufacturing Practice for Drugs*, and in May 1997, it issued *provisions for Good Manufacturing Pratice for production of blood components at Blood and Plasmapheresis Centres to be used as starting material for drug production.*(60,61) This document addresses, e.g. general standards concerning quality systems, personnel, organization, facilities, equipment, and documentation in blood and plasma establishments. GMP requirements in blood and plasma collection and component manufacture is described in detail, from control of basic material (raw material, reagents, packaging), donor selection, and blood collection, to manufacture of blood components, and release, storage, and transport of these components. Standards for managing complaints, adverse events, and recalls are also included. For example, the Medical Products Agency, the National Swedish Board of Health and Welfare, and the manufacturer shall be informed in cases of a confirmed reaction to a virus test.

3.5 Concluding Remarks

The use of plasma derivatives always involves a risk, even if it may be quite small. The use of products in intramuscular administration is considered to involve significantly less risk than products used intravenously. Intravenous administration of blood products is, however, usually performed on serious indications. The products

that have been approved for the market meet the standards of ”medical appropriateness”, ie the risks/side effects are not greater than the positive effects.

The conclusions gain in strength when one considers the safety measures observed throughout the entire process, from donors to end product. The tests are sensitive, and validated methods are used to purify the various active substances to inactivate or separate potentially contaminating viruses. It cannot be ignored that even in the future we may be faced with problems caused by yet unknown viruses or other contagious agents, similar to the problems that appeared with HIV/AIDS during the first half of the 1980s,.

To maintain acceptable, long-term safety in the use of plasma derivatives, it is necessary to apply scientifically accepted standards in a harmonized manner. National regulations differ to some extent within EU. It should be a requirement that all products, whether manufactured within EU or imported, comply at least with the standards specified by the European Pharmacopoeia and the central regulatory authority within EU, EMEA/CPMP. Not until then can safety be guaranteed or can fair competition prevail between imported products and those produced within the European Union. The recommendations concerning the screening of donated blood and the suitability of blood and plasma donors, upon which the EU Council of Health Ministers in June, 1998 reached political agreement, represent an important step in European harmonization.

4 Plasma Sufficiency in Sweden and Other EU Countries

4.1 Structure and Organization of Plasma Activities

The most recently published data from the National Swedish Board of Health and Welfare cover Swedish plasma activities in 1996.(18) To acquire further information, the Working Group used two questionnaires to collect data on the scope and costs of plasma activities; one surveyed plasmapheresis activities, and the other attempted to quantify the amount of recovered plasma delivered to the fractionation industry. (For a more detailed description of the questionnaire data, see Chapter 5, Economic Aspects).

The data show that plasma donation is a routine activity at 25 of the 88 active blood and plasma establishments in Sweden. Plasma donation on a large scale occurs in the 9 regional blood establishments and in a few blood establishments at county hospitals. Plasma donation in separate, non-hospital facilities occurs, e.g. in Karlstad and Stockholm. ”Citytappen”, which is located in Stockholm, is not managed by the county, but by a private plasma fractionation company (Pharmacia & Upjohn).

Data on the collection and use of plasma and plasma products in EU countries have been published by the European Commission for 1991 and 1993.(36,5) An additional report will be compiled for 1995. The 1993 report contained only limited data from Sweden, Finland, and Austria. Data from the private plasma industry is unavailable since the European Association of the Plasma Products

Industry (EAPPI) announced, on behalf of its members, that data could not be released due to trade secrets.

The Commission's reports provide little data on the structure and organization of plasma collection in Europe. Other sources show that large plasma establishments managed mainly by private industry, without direct ties to the health services, exist mainly in Germany and Austria. During the early 1990s, transfusion activities became highly centralized in several EU countries, e.g. Great Britain and France, and plasma fractionation is now managed by a few national, non-commercial fractionaters.(62) Although transfusion services, including plasma collection, are managed as a public service in these countries, it is organizationally distinct from the other health services. The Red Cross has traditionally played a monopoly-like role regarding blood and plasma activities in some European countries, mainly Finland and the Netherlands.

4.2 Access to Donors

From an international perspective, Sweden has had good access to blood and plasma donors. This has not been a natural occurrence, but has been the result of extensive recruitment campaigns and continuous information from the organizations engaged in these activities.

In 1996, Sweden had approximately 20 000 plasma donors and over 400 000 registered blood donors (including plasma donors). This corresponds to 45 donors per 1000 inhabitants. During the 1990s, there has been a relatively stable number of blood donors who have been active per calendar year, between 210 000 and 235 000. The number of newly registered donors increased from 28 000 donors in 1992 to 38 000 in 1996. Since plasma donation was not included in the registries before 1994, longitudinal trends cannot be shown for this activity.

The following numbers of blood and plasma donors have been reported within EU: Denmark reported 268 000 donors in 1993 (52/1000 inhabitants), Finland reported 170 000 (34/1000), the

Netherlands reported 656 000 (43/1000), Germany reported 2 700 000 (33/1000), France reported 2 302 000 (40/1000), and Great Britain reported 2 522 000 (44/1000). Many of the countries did not specify whether the donations were whole blood or plasma.

Compared to the situation in 1991, the number of blood donors in EU during 1993 had been at a stable level, approximately 10 million (Sweden, Finland, and Austria not included, data was also missing from Spain and Greece). Notable changes in access to blood donors could be noted only in Denmark (-6%) and in Germany (+12%).

Specific reports on the number of plasma donors in 1993 were provided by six EU countries – Ireland, Italy, Luxembourg, the Netherlands, Portugal, and Great Britain. In these countries, the number of plasma donors had increased by 18% between 1991 (117 000) and 1993 (139 000). The increase was most marked in Italy (+42%) and the Netherlands (+35%).

4.3 Supply of Plasma for Fractionation

According to the report from the National Swedish Board of Health and Welfare, 266 011 kg of plasma were produced in Sweden in 1996. 256 000 kg of plasma were sold as source plasma for fractionation. 147 000 kg of plasma for fractionation had been collected via plasma donation, whereof apheresis plasma represented approximately 55% of the total plasma quantity and 57% of the plasma for fractionation.

The quantity of apheresis plasma collected has steadily increased over the past 15 years. Figure 4:1 illustrates the trend between 1982 and 1996.

Figure 4:1. Annual quantity of manufactured apheresis plasma. 1982-1996. *All the figures and diagrams in this report are only presented in the printed edition.*

Source: Survey of blood supply in Sweden, 1996. The National Swedish Board of Health and Welfare and the Swedish Society for Transfusion Medicine. Örebro: The National Swedish Board of Health and Welfare, 1997.

The total quantity of collected plasma, like the quantity of apheresis plasma varies considerably among the different health care regions in Sweden (Table 4:1). Uppsala/Örebro had the largest plasma production of the six regions, over 80 000 kg in 1996. Most of this quantity, over 64%, was of apheresis plasma.

Table 4:1. Quantity of collected plasma and apheresis plasma per health care region, 1996.

Region	Total plasma	Plasma/1000 inhabitants	Apheresis plasma	Apheresis plasma/ 1000 inha-bitants	Share of apheresis plasma
	kg	kg	kg	kg	%
West Sweden	26 130	15,8	4 944	3,0	19,0
Southeast	29 620	30,5	18 322	18,8	61,9
South	29 953	19,2	8 759	5,6	29,2
Stockholm	57 520	32,2	35 165	19,7	61,1
North	41 961	45,5	28 245	30,7	67,3
Upps./Örebro	80 827	41,5	51 837	26,6	64,1
Total	266 011	30,1	147 272	16,7	55,4

The largest plasma production in relation to the population base, however, was recorded in the northern region, 45.6 kg per 1000 inhabitants, of which 30.7 kg (over 67%) was apheresis plasma. Plasma production was lowest, both in total quantity and quantity of apheresis plasma, in the western region.

The questionnaire survey of the Working Group shows large differences among hospitals in the amount of apheresis plasma collected. Isolated blood/plasma establishments reported annual collection volumes between 830 kg and 16 000 kg, with a median of approximately 2300 kg.

Among the regional blood establishments, the reported quantities varied between 1600 and 12 000 kg. At the county hospital level, the corresponding variation ranged between 830 kg and 16 000 kg. At the county district level, the largest amount of collected apheresis plasma was 5100 kg per year.

4.4 Supply Balance

Chapter 2 presented a definition of self-sufficiency in blood plasma and plasma products and described the difficulties in estimating supply levels. In 1996, the amount of plasma for fractionation in Sweden exceeded, for the first time, Swedish demand for factor VIII. According to estimates by the National Swedish Board of Health and Welfare, this corresponds to approximately 185 000 kg of source plasma (Figure 4:2). Since 1990, Sweden has been viewed as self-sufficient, i.e. the quantity of plasma delivered has been equal to or greater than the estimated need.

Figure 4:2. Plasma needed for national self-sufficiency based on fractionation and deliveries from Swedish blood establishments. 1985-1996.

Source: Survey of blood supply in Sweden, 1996. The National Swedish Board of Health and Welfare and the Swedish Society for Transfusion Medicine. Örebro: The National Swedish Board of Health and Welfare, 1997.

Estimates of self-sufficiency depend on the level of industrial exchange in factor VIII and the gradual transition to alternative, genetically engineered products. If the industrial exchange level is assumed to be 20% – instead of 23% as estimated by the National Swedish Board of Health and Welfare – the calculated need for plasma in Sweden would be higher, approximately 213 000 kg. On the other hand, the transition to recombinant alternatives would decrease the need for plasma derived factor concentrates. In the future, it is possible that another type of plasma product, e.g. the group of immunoglobulins, will determine the need for fractionation plasma.

As mentioned earlier, the European Commission has actively monitored the collection and use of blood, plasma, and plasma products in the member states since the late 1980s. A progress report from 1993 noted that while EU was nearly self-sufficient in blood and blood components at the time, there was a severe shortage of plasma in EU as a whole. According to estimates by the Commission, the amount of plasma collected for fractionation was approximately 3 720 000 kg, while the estimated need was between 5 110 000 and 6 140 000 kg, depending on the level of FVIII recovery in the fractionation process.(5) From 1991 to 1993, the shortage of plasma in the European Union had increased.

The Commission's estimate is based on the reported consumption of factor VIII in the 12 member states in 1993. On average, this represents a demand for factor VIII which is below the current demand in Sweden. If the consumption in Europe as a whole had been equivalent to the Swedish level, the self-sufficiency situation in Europe would have been even less favorable.

The self-sufficiency situation in Europe can be further illustrated by the European Commission's statistics on the import and export of plasma. These statistics show that in 1993, EU as a whole imported 2 080 000 kg of plasma from countries outside the Community, mainly from the United States. Four member states were responsible for the imported plasma; France, Italy, Germany, and Spain. Compared to 1991, imports to France had decreased substantially, to 700 kg. Imports to Italy had decreased, but still

accounted for 996 000 kg. However, imports to Germany and Spain had increased and accounted for 741 000 kg and 345 000 kg of source plasma, respectively. The Netherlands, which in previous years had reported on the import of plasma from countries outside EU, did not provide information on imports in 1993.

The statistics for 1995 reflect a change in the supply of plasma within EU, due to the inclusion of data from Austria, Sweden, and Finland. Among these countries, Austria is a large importer of source plasma. However, plasma imported by Austria is used to manufacture drugs which are mostly exported, to other EU member states and other countries. In 1995, industry in Sweden imported 57 000 kg of plasma from other EU countries and 10 000 kg of plasma from the United States. During the same year, an estimated 65 000 kg of plasma was exported from Sweden, entirely to countries within EU.

In the future, the gradual transition to recombinant factor VIII is expected to have a positive influence on the supply balance within EU. Concurrently, however, increased demand for other plasma products, mainly immunoglobulins, may have a negative impact on this balance.

4.5 Demand for Plasma derived Drugs

4.5.1 Coagulation Factor VIII

Until now, factor VIII has been the plasma product used to predict plasma production. Hence, comparing European consumption levels is of particular interest. The estimate presented above, concerning the supply in Sweden, is based on a current consumption level of approximately 4.3 IU factor per inhabitant and year. Table 4:2 shows this level to be relatively high by international comparison.

Table 4:2. Use of coagulation factor VIII in EU, 1993.

Country	Total consumption	Consumption/ inhabitant
	IE x 10^6	IE
Belgium	32.8	3.2
Denmark	17.0	3.3
Finland	10.6	2.1
France	131.0	2.3
Greece	6.0	0.6
Ireland	6.0	1.7
Italy	114.0	2.0
Luxembourg	1.8	4.6
The Netherlands	53.6	3.5
Portugal	7.3	0.7
Spain	81.6	2.1
Great Britain	140.0	2.4
Sweden	38.1	4.3
Germany	330.0	4.1
Austria	no data	no data

Sources: European Commission DGV, National Swedish Board of Health and Welfare.

The wide variations in consumption between Sweden, Germany, and Luxembourg on one hand, and the remaining EU countries on the other, are mainly the result of differences in the prophylactic treatment of hemophiliacs. While prophylactic treatment is standard practice in Sweden, in some countries it is viewed as research. In these countries, patients with hemophilia are not treated with factor VIII prior to the onset of joint bleeding or other symptoms. In Sweden, treatment goals have been set at a higher level, and prophylactic treatment is viewed as important to the quality of life of hemophiliacs. Care of hemophiliacs in Sweden is delivered by a few specialized centres, which is why treatment policies vary insignificantly within the country.

In 1996, the total consumption of factor VIII in Sweden, including recombinant products, corresponded to approximately 250 million SEK.

4.5.2 Albumin

In recent years, the use of albumin has been frequently debated, e.g. in the Journal of the Swedish Medical Association. The basic issue has been the need for albumin in relation to less expensive plasma volume expanders to treat fluid loss which may arise, e.g. in conjunction with major surgery.

Publication of the Sanguis study, showing data on wide variations among member states, e.g. in the use of albumin, drew attention to the issue in EU.(19) The European Commission's statistics for 1993 continue to reflect extensive variations in this respect, although the data are difficult to interpret and, in many respects, insufficient. The Sanguis study concluded that utilization of the plasma products studied was driven more by local education and treatment traditions than by scientific evidence. Several healthcare researchers have observed that uncertainty about scientific knowledge may be an important contributor to regional variations in treatment practice.(64,65)

In Sweden, statistics from the National Corporation of Swedish Pharmacies show extensive variations in use of albumin among the county councils (Table 4:3). A 5-year trend shows that while consumption in some county councils, e.g. Uppsala and Malmöhus, is increasing, consumption in others, e.g. Stockholm and Örebro, is decreasing. To some extent, these trends can be explained by the organization of regional medical services, particularly in the treatment of burns.

The total monetary value of albumin consumption in Sweden in 1995 was approximately 70 million SEK.

Source: Delivered inventory; statistics from the National Corporation of Swedish Pharmacies

4.5.3 Immunoglobulins

Sales statistics show that 525 kg of immunoglobulins were used in Sweden in 1996 (300 kg for intramuscular/subcutaneous use and 225 kg for intravenous use). Home treatment, involving subcutaneous pumps, of patients with immune deficiency disorders accounted for the large share of intramuscular sales.

The total consumption of immunoglobulins for extravascular and intravascular use in 1996 corresponded to a cost of approximately 90 million SEK. However, consumption – and hence costs – varied considerably across Sweden. This is illustrated by the cost data on immunoglobulins for intravascular use (Table 4:4).

It is difficult to estimate the optimum current and future utilization of immunoglobulins. There are several well-established indications, and additional ones can be seen on the horizon. At the same time, initial optimism has faded somewhat concerning potentially broad applications for autoimmune conditions.

Among other reasons, estimates are difficult because approximately 30% of current volumes in Sweden are used in clinical trials, and there is also a risk that prices for plasma-derived products will increase if the companies are unable to find markets for all components, especially factor VIII.

Source: Delivered inventory; statistics from the National Corporation of Swedish Pharmacies

4.6 Concluding Remarks

In Sweden, the collection of blood plasma is almost entirely under the control of the health services. A large private plasma establishment has been in operation since 1991, and in recent years a few private collection centres have been contracted by some county councils.

Plasma establishments operated by private industry, without an affiliation to medical services, are common in some EU countries, especially in Germany and Austria. Some member states, such as Great Britain and France, centralized transfusion activities during the early 1990s. Although plasma collection in these countries is under public management, it is organizationally separate from other medical services. In some EU countries, mainly Finland and the Netherlands, the Red Cross has traditionally held a monopoly-like position in blood and plasma services.

Sweden has enjoyed relatively good access to plasma donors as a result of information and recruitment campaigns. In 1996, Sweden reported a production of 266 011 kg of plasma, and 256 000 kg of plasma were sold as source plasma for fractionation. 147 000 kg of plasma for fractionation had been collected by plasma donation, whereof apheresis plasma comprised approximately 57% of the plasma for fractionation. The amount of plasma for fractionation in 1996 exceeded, for the first time, the Swedish demand for factor VIII. According to estimates by the National Swedish Board of Health and Welfare, this corresponded to approximately 185 000 kg of source plasma.

There is a severe shortage of plasma within the EU as a whole. According to the Commission's calculations, in 1993 approximately 3 720 000 kg of plasma were collected for fractionation while the estimated need was between 5 110 000 and 6 140 000 kg, depending on the industrial exchange level. From 1991 to 1993, the shortage of plasma within the union had increased, and extensive import of source plasma from the United States was still required.

Estimates of self-sufficiency are sensitive to variations in demand for end products manufactured from source plasma. The

Commission's description of self-sufficiency is based on the consumption of factor VIII in the 12 member states in 1993. This reflects a lower average demand for factor VIII than what is currently the case in Sweden. If the level of consumption in Europe as a whole had corresponded to the Swedish level, the European self-sufficiency situation would have been even less favorable.

In the future, the gradual transition to recombinant factor VIII is expected to reduce the demand for plasma derived products and positively influence the balance in supply. Concurrently, increased demand for other plasma products, especially immunoglobulins, may negatively affect the balance. The scientific evidence for using coagulation factors, albumin, and immunoglobulins in various conditions is unclear and needs further study before a valid prognoses of the future is possible.

5 Economic Aspects of Plasma Services

5.1 Factual Base

A systematic review of the published literature, Swedish and international, has been conducted addressing the financial aspects of plasma collection.

One study compares the costs for blood and plasma services in France, Belgium, and Great Britain.(62) The cost estimates concern the prevailing circumstances in the respective countries, hence the results are difficult to compare with Swedish data. The authors of a Canadian study try to theoretically describe the marginal costs which arise when the capacity of plasma services gradually expand. Actions taken against bottlenecks in production, such as increasing the staff and the number of blood-collection machines, are presented.(66) Some articles address the costs related to self-sufficiency in blood and plasma.(67,68,69) Compensation to donors is the focus of a few articles.(70,71) Some of the articles describe technical accounting problems associated with the distribution of costs among various blood products.(72–79) The contents of all of the articles referred to above are, however, more of a discussion on perceived problems than an accounting of empirical fact. Most of the articles address blood collection, while plasma collection is less frequently addressed.

Hence, the review reveals a nearly complete lack of literature providing relevant cost information. Articles addressing cost variations in the chain of production are also lacking. No studies are

available on the association between collection volumes and production costs.

Representatives dealing with issues of blood and plasma supply in EU countries have been surveyed by letter about the costs for source plasma, etc. Cost data on plasmapheresis collection are considered to be a trade secret in many countries, and these figures are not released. Responses containing data on the costs for plasma collection were received from a few EU countries. The only cost information on plasma collection in the United States is based on a single plasma establishment.

Certain problems are associated with the relatively sparse data obtained from other countries. Data from two or more sources are often inconsistent. Due to variations in exchange rates among currencies, it is also difficult to convert cost and price data from foreign currency to Swedish kronor (SEK). Foreign currencies have been converted to SEK based on the exchange rate in January 1998. One U.S. dollar (USD) at the time corresponded to 8.00 Swedish kronor (SEK), and one German mark (DEM) corresponded to approximately 4.50 SEK.

In Sweden, data on costs, revenues, and utilization of capacity of plasma services have been obtained from two mail questionnaires directed to the blood establishments across the country. One questionnaire addressed apheresis activities and the other addressed the manufacture of recovered plasma. The data on plasma activities which are presented in this chapter are based largely on data from the 19 centres which gave a relatively complete accounting of costs in their responses to the questionnaire.

5.2 Price of Plasma

According to data from a pharmaceutical company, approximately 230 tons of plasma were delivered from the Swedish blood establishments to the pharmaceutical industry in 1995. Of this quantity, 135 tons were source plasma and 95 tons were recovered plasma.(80) The price of domestic source plasma in 1996 was

approximately 1050 SEK to 1100 SEK per kg. Since mechanical collection involves less dilution with anticoagulant solution, the price for this plasma is usually somewhat higher than for manually collected plasma. In 1997, the price paid by Pharmacia & Upjohn in Sweden fell to approximately 950 SEK per kg source plasma. Baxter (Immuno) paid approximately 760 SEK to 880 SEK, VAT excluded.

Recovered plasma from the blood establishments entails different prices depending on the quality. For recovered plasma frozen within 6 hours (FFP-1), the price in 1996 was somewhat over 700 SEK, while the price for plasma which had been frozen within 24 hours (FFP-2) was somewhat below 600 SEK. The percentage of lower quality plasma is very small.

Table 5.1 presents data from the European Association of Plasma Producing Industry (EAPPI) on the pharmaceutical companies' purchase price for source plasma and recovered plasma, by country.(81) The market price for imported source plasma from the United States was 640 SEK to 720 SEK per liter. The estimated price for European source plasma was approximately 50% higher than the price of American source plasma.

The price reported for Germany, 1040 SEK, is somewhat higher than the corresponding information from another source, approximately 830 SEK to 1010 SEK. The difference may be due to calculations based on different exchange rates. The price reported by EAPPI for source plasma in Sweden, 130 USD, corresponds to the price of approximately 1050 SEK that Pharmacia & Upjohn paid per kg in 1996. It is clear from the price comparison for recovered plasma that the price interval in Sweden was somewhat higher than in the United States, but lower than in Germany.

Table 5.1 Purchase price per liter of source plasma and recovered plasma (FFP) in USD and SEK, by country, 1996.

Plasma	Sweden		Germany		Europe		USA		Japan	
	$	Kr	$	Kr	$	Kr	$	Kr	$	Kr
Apheresis	130	1.040	130	1.040	120	960	80-90	640-720	140	1.120
FFP	–	*600-700*[a]	110	880	–	–	75	600	–	–

Sources: EAPPI (Regulatory Affairs Symposium, Amsterdam 1996, MRB) (81); USD/SEK ~8.00 January 1998; *Questionnaire, quantity in **SEK/kg**.*

5.2.1 VAT

In plasma sales, the price varies depending on whether or not VAT is included. Until 1995, the pharmaceutical company which purchased the plasma could deduct a so-called fictive VAT from the purchase price. When the fictive VAT was discontinued, this meant in practice that the purchase price of the industry for domestic plasma increased by an amount corresponding to the VAT. The price of plasma from blood establishments was then in a worse competitive position compared to foreign plasma.

The regulations of the National Swedish Tax Board (RSV) specify that human blood and organs are exempt from VAT.(83) Some blood establishments follow a practice that places plasma in the same category as blood. A large quantity of plasma is used directly in hospitals in conjunction with treatment. The plasma sold to the pharmaceutical companies is further processed into pharmaceuticals by the industry. Prescription drugs are exempt from VAT. Hence, when drugs based on blood products are purchased by the counties, VAT is not included in the price. Since drugs purchased from industry are exempt from VAT, it has been considered logical to exempt other products in the refinement of

plasma from VAT. This interpretation has resulted in a practice whereby VAT is not debited in the plasma trade.

However, the regulations are interpreted in different ways, and practice varies. According to the ”Guide for VAT, 1996” by the National Swedish Tax Board, sales of plasma should not be exempt from VAT.(84) Consequently, the representatives for blood establishments have expressed concern that the revenue obtained from selling plasma will no longer cover the costs, since a part of the revenue must be shown as VAT and paid to the tax authorities.(85) If sales of source plasma are no longer exempt from VAT, the accounting practices must be changed.

5.3 Cost of Plasma Collection in Sweden, Europe, and the United States

According to the questionnaire, the average cost of production for source plasma in Sweden was 1028 SEK per kg in 1996. The price range for American source plasma, according to the pharmaceutical industry, varies between 640 SEK and 720 SEK, which includes a profit margin. This information suggests that the cost for plasma collection in the Unites States is substantially lower than in Sweden.

In Germany, the average cost per liter source plasma at the plasma collection banks, is reported to be approximately 900 SEK.(82) Furthermore, the data from Germany show that some banks have considerably higher costs.(86) This indicates that there may be large variations in costs among collection centres in Germany. The Belgian Red Cross reported data for 1996 based on an average cost *per unit of 630 ml* source plasma.(87) After conversion, the cost corresponds to approximately 1250 SEK *per liter*.

Table 5.2 compares the average cost per kg source plasma in Sweden, Germany, and the EU according to the percentage distribution for different types of costs. The German data are based on

privately managed plasma collection banks. The EU data are based on company information from several countries.

Table 5.2 Comparison of average costs for collecting source plasma in Sweden, Germany, and EU, distributed in percent according to different types of costs, 1996

Type of Cost	Sweden %	Germany %	EU %
Material	26	21	23
Laboratory tests	21	5,5	10
Donors	12	33	14
Personnel	26,5	30	32
Facilities	4	6,5	–
Other	10,5	4	20
Total	100	100	100
Total SEK	*1 028*	*900*	*u.s*

Sources: Questionnaire; Regierungsdirektor F v Auer, Germany (88); EAPPI(81).

The relative distribution of different types of costs are both similar and dissimilar. *Costs for material* and *personnel* always represent a substantial share of the average cost. They are also similar in size.

Costs for laboratory tests differ widely. The data show that the cost of laboratory tests in Germany is relatively low, 5.5%. This figure probably includes only the costs for kits and some equipment. Other German cost data reflect a substantially higher percentage for this type of cost. The figure in Sweden is 21%, which probably includes staff costs in microbiology laboratories. The figure may also be influenced by high internal prices on laboratory services.

The percentage for *donor compensation* is similar in Sweden and EU. The data for EU as a whole, as with Germany, include the costs for recruiting donors. This, and the fact that the German data are from private centres with paid plasma donors, explains the relatively high percentage of costs attributed to donor compensation

in Germany. *Costs for facilities* are relatively equal in Sweden and Germany. This post, however, represents a small share of the total average cost.

A comparison of individual collection units in Sweden, Germany, Austria, and the Unites States shows that the costs for consumables and laboratory tests were twice as high in the European banks as compared to the U.S. banks. Donor compensation was relatively high in Germany, both in absolute numbers and related to the total average cost per kg of plasma. In Sweden, donor compensation (including refreshments) was lower, approximately 120 SEK per kg, which is similar to that reported from the United States. Approximately 80% of the American plasma donors are paid. In the U.S., compensation per donation is approximately 75 SEK to 135 SEK.(90)

The percentage of the total costs spent on personnel in Sweden, Germany, and the EU is 25% to 32%, which is considerably higher than that reported by the U.S. plasma centre.(89) The Sweden regulations concerning the formal training of blood establishment staff, and the staffing ratios in relation to the number of donors, may explain the higher personnel costs in Swedish plasma centres compared to those in the United States.

The private plasma establishments in Germany produce, on average, approximately 10 000 to 12 000 kg of plasma annually. On average, 650 ml of plasma (including anticoagulants) is collected from an individual on one occasion. Plasma centres in Germany generally receive plasma donors for 37 hours per week (4 days per week). As a regulation, the occupancy rate is 70% to 80%. In the United States, the private plasma centres are open 95 hours per week (6 to 7 days per week). It has been reported that the average quantity collected from an individual is 830 ml of plasma (including anticoagulant solution) per collection session.(82) The responses to the questionnaire show that, in Sweden, plasma donations are received, on average, 37 hours per week (Monday through Friday during a normal week).

5.4 Variations in Costs Among Swedish Plasma establishments

Questionnaire responses concerning the costs for plasma collection were received from 63 blood establishments, or 70% of the blood establishments in Sweden. Among the 25 blood establishments that reported collecting plasma, 19 gave relatively complete cost information. The blood establishments answering the questionnaire were distributed in a way similar to the frequency of plasma donations reported in ”Survey of Blood Supply in Sweden, 1996”, issued by the National Swedish Board of Health and Welfare in collaboration with the Swedish Society for Transfusion Medicine.(18) This report includes all blood establishments in Sweden. The degree of similarity between the reports indicates that the questionnaire responses are probably representative for the blood establishments offering plasma services.

Fewer responded to the questionnaire on recovered plasma, i.e. 49 units, or 54% of the possible respondents. The distribution of blood establishments, based on the number of blood donations, was similar to that found in the report from the National Swedish Board of Health and Welfare. Hence, the responses were judged to be representative.

5.4.1 Problems in Cost Accounting

The data collected on the production costs for source plasma are divided into types of cost, such as personnel, consumables, compensation, and refreshments during plasma donation, laboratory tests, facility costs, capital equipment costs, etc, and other costs. Included among other costs are general services, transportation, donor recruitment, additional general administration costs, and other shared costs in hospitals.

A problem that can be identified from the responses concerns the distribution of costs for plasma activities. Some of the units are organizationally categorized under hospital laboratory services,

where blood and plasma activities are not specified in the cost accounting of the hospital. Other examples of problems related to cost distribution involve situations where it is impossible to account for certain types of costs incurred by plasma services, e.g. personnel costs, facility costs, equipment costs, and shared operational costs for the hospital. Wide variations in local practices make it difficult to compare the plasma activities of different blood establishments. Information on equipment costs was lacking in several responses. Some purchasing arrangements exist where suppliers install the equipment free of charge but receive payment via contracts where the purchaser agrees to buy a certain quantity of consumables at a given unit price.

Given the problems mentioned above, a general presentation has been compiled from the data received from all units offering plasmapheresis services. A more detailed accounting is provided on the 19 units that reported more complete cost information.

5.4.2 Wide Variations in Plasma Collection Volumes

There is a close association between the number of patient tables and plasma collection machines, and the number of collections at blood establishments. Concurrently, however, there are examples of wide differences in number of collections among blood establishments having the same number of tables. In all units responding to the questionnaire, plasma is collected using automated equipment. One of the units also reported manual collection. Two of the 25 units offering some type of plasmapheresis collection reported very limited activity.

Normally, a plasmapheresis unit has 5 machines. During a year, nearly 4000 collections are performed, yielding approximately 2300 kg of plasma. The differences between units reporting relatively little activity and those reporting more were, however, great (Table 5.3). One unit collected only 9 kg of plasma in 15 collections and another unit collected 60 kg in 225 collections, while the largest

collected nearly 16 000 kg in over 25 000 collections. Half of the units, those between the first and third quartile, are in the range from 2800 collections per year and 1600 kg of plasma to 9600 collections/5.900 kg of plasma.

Table 5.3. Number of collections and collected quantity of source plasma in 25 blood establishments. Median value and range between minimum and maximum values, 1996

	Minimum	First quartile	Median	Third quartile	Maximum
Number of collections	15	2 780	3 778	9 632	25 568
Quantity, kg	9	1 636	2 314	5 930	15 865

In the 19 blood establishments reporting cost information, no significant difference in cost is evident between large and small blood establishments. The four blood establishments reporting more than 15 000 collections per year have relatively low costs per kg source plasma, but the corresponding cost levels occur also in blood establishments with significantly fewer collections annually (Diagram 5:1).

Diagram 5:1. The relationship between collected source plasma and number of collections in 19 blood establishments, cost in SEK per kg, 1996.

5.4.3 Opening hours

On average, a blood establishment offering plasma services receives donors for 37 hours per week, Monday through Friday. Opening hours vary, both in the number of hours per day and the number of days per week. Half of the units are open between 33 and 42 hours per week, while the remaining units are open somewhat fewer or more hours. In the summer, the units are closed either all or part of the time from Midsummer to mid-August, or services are greatly reduced during this time. The median days a unit is open is 225 days per year.

5.4.4 Costs per kg of Source plasma

In the 19 blood establishments for which cost data were analyzed, the *median cost* per kg source plasma was 1021 SEK. The lowest reported cost was 782 SEK per kg while the highest was 1386 SEK. The interval between the first and third quartile was from 939 SEK to 1081 SEK.

The estimated *mean cost* was 1028 SEK per kg. A 95% confidence interval around this mean value is between 962 and 1093 SEK. This can be compared to preliminary data concerning the average cost per kg of plasma in eight larger blood establishments in Sweden, 938 SEK.(91) However, costs for investment in equipment, etc, were not included. Furthermore, it is uncertain to what extent all relevant personnel costs have been included. The lack of these data and the limited selection probably means that the cost differences between the two sources are actually not so great.

Cost per kg of source plasma, by type of cost, is presented in Diagram 5:2. It is evident that several of the blood establishments which have a lower total cost per kg have omitted the costs for equipment. Other examples show that costs for facilities or other costs have not been included, e.g. percentage of shared operational costs in the hospital, administration, etc. The magnitude of other costs also varies widely. The blood establishment with the highest total cost has extremely high ”other costs” in comparison to the other blood establishments. Furthermore, the same unit reports extremely high personnel costs.

Diagram 5:2. Total cost and costs divided by type of cost per kg of collected source plasma in 19 blood establishments, 1996.

The blood establishment with the lowest total cost has consciously omitted, eg joint costs to describe the ”essential activities”. Facility costs have been reduced by locating services in older sites with low rent.

It appears as if the blood establishments with higher total costs had relatively high costs for personnel and/or laboratory tests. In some cases, these blood establishments also reported relatively high ”other costs”. There is also a trend toward somewhat higher costs for material among units with a high total cost. A factor which may be partly responsible for the differences in production cost per kg of source plasma is that blood establishments with relatively low costs generally collected a somewhat larger quantity of plasma per collec-

tion session than units with higher costs. Volume differences were, however, small.

5.4.5 What is a Reasonable Cost?

What is a reasonable cost per collection and per kg collected plasma? For the variable costs, material, laboratory tests, and compensation to donors, a rough estimate of a ”reasonable” cost can be made, at least for some of the items. For the remaining cost items, personnel, facilities, equipment, and other costs, it is more difficult to estimate such a cost.

In *costs for material*, a collection kit is estimated to cost approximately 120 SEK to 130 SEK. To this can be added a smaller sum for various consumables in association with plasma collection. In total, the material costs per collection could be estimated at approximately 140 SEK to 150 SEK. If the blood establishments collect slightly over 600 ml, including anticoagulant solutions and some loss due to failed collections, etc, the cost per kg should not exceed 250 SEK.

In most cases, the material costs reported from the blood establishments exceed this ”reasonable” cost. In some cases, this can be explained by equipment costs being added to the price for disposable kits due to financial agreements with the supplier. Hence, the cost for material is higher while costs for equipment is lower. The deviations are, however, not explained by lower than normal collection volumes per collection session.

The cost for routine *laboratory tests* per collection should normally not exceed 80 SEK. If tests for syphilis, ALAT, hemoglobin, etc are included, the cost is slightly over 100 SEK. Using the same basis for calculation as above, this corresponds to approximately 160 SEK to 170 SEK per kg. The blood establishments’ costs for laboratory tests usually exceed the ”reasonable” cost, in many cases by relatively large sums. A possible reason for this might be that larger or smaller sums for personnel costs have been added to the laboratory services, depending on the organization of the hospital and how the costs are distributed to different units. The internal

prices for laboratory services may exceed the actual costs. It is not clear from the responses how the accounting was done at the respective blood establishments.

Donor compensation amounts to 60 SEK per session. If costs for refreshments, sandwiches, beverages, etc are added, the cost probably reaches 75 SEK to 80 SEK. The corresponding maximum cost per kg would then be 130 SEK to 140 SEK. The estimated cost for donor compensation, etc is exceeded only in a few cases and then only marginally. In most blood establishments the reported amount is below the reasonable cost, due to not reporting the cost for refreshments.

Personnel costs are a relatively large cost item, and there are relatively large differences among units. The information given in the questionnaire, however, does not explain the deviations. A significant factor may be the distribution of personnel costs. Do the personnel costs apply only to the reporting unit, or do the figures also include personnel costs for non-plasma activities? The latter would apply to, eg the blood establishment with the highest total cost per kg, attributed largely to extremely high personnel costs.

Relatively low sums are reported for the remaining cost items, *facilities, equipment, and other costs*. The percentages, however, vary widely among blood establishments. In some cases, information on costs, eg for equipment, has been left out entirely. The reason given is that the investment cost for the equipment, once acquired, is completely written off from an accounting perspective, and hence is no longer taken up as a cost in the accounting process. In some cases, the facility costs for plasma activities have been difficult to specify. The yearly rent per square meter ranges between 1000 SEK and 2000 SEK for most blood establishments. The average is somewhat over 1400 SEK. Due to differences in the size of the facilities and rent per square meter, facility costs vary widely among blood establishments. The cost item is relatively small in relation to the total cost. The same is true for ”other costs”.

5.4.6 Significance of Plasma Collection for the Blood establishment

The revenue from sold source plasma must, in the long run, cover the blood establishments' costs of collecting plasma. Many blood establishments covered their costs in 1996, but in several units the costs of plasma activities were higher than the revenues. The revenue/cost ratio for source plasma varied between 0.77 and 1.35, with a median of 1.03. Twenty-five percent of the units had a ratio of 0.77 to 0.97, i.e. their income was somewhat lower than their costs.

In the blood establishments that collect plasma, this activity normally represents a significant element in the activities of the entire blood establishment. Total revenue from sales of source plasma, which is offset by almost equally as large costs, amounts on average to 21% of the total costs of the blood establishment. If one adds the total revenue the blood establishments receive for recovered plasma, often more than 10% in relation to the total cost of the unit, it can easily be understood that a substantial share of blood establishment activities and the resources expended are covered by the revenue from plasma sales.

5.5 Association Between Production Cost and Collection Volume

The cost of collecting plasma depends partly on how much can be collected from a donor on a single occasion. The greater the volume collected per collection session, the fewer collection sessions required to obtain one kg of plasma. If the variable unit prices per collection remain unchanged at different volumes, this means that the variable cost per kg for material, laboratory tests, and donor compensation, decreases as the collection volume is increased. If the total fixed costs are assumed to be constant, and the total quantity of plasma increases, the fixed cost per kg is lower. When the number of collections is constant or increases concurrently with an

increase in volume per collection, there is a greater potential for reducing both the variable and fixed costs per kg.

5.5.1 Hypothetical Conditions

There is no empirical basis for describing the relationship between the cost of production and different collection volumes per collection session. Lacking this, such an association can be studied by means of a theoretical example. An advantage in using a theoretic model is that one can more clearly observe how the cost of production is influenced by a change in a single variable (plasma volume) since other variables remain constant. A disadvantage is that one can question whether or not the calculation is realistic. Also, interpretation of the results may be difficult since it should be related to the actual activities of the blood establishments.

The data in the calculation is based on the questionnaire responses from 19 blood establishments on cost per collection and per kg of plasma and the average volume collected per session. In the calculation, costs for material, laboratory tests, and donor compensation have been viewed as variable costs while personnel, facilities, equipment, and other costs have been viewed as fixed costs. The calculation aims to describe the circumstances in the short term. The total fixed costs are presumed to be constant. To simplify the calculation, one liter of plasma is assumed to weigh one kg.

Two different outcomes have been calculated. One is based on the assumption that the *number of collections* by a blood establishment coincides with the number reported in the questionnaire. If the volume per collection session is increased, the total quantity of plasma collected is greater.

The second is based on the assumption that the *total quantity of collected plasma* in a blood establishment coincides with that reported. If the collection volume per session increases, fewer collections are required to achieve the given total quantity.

In both examples, the cost in real collection volume per session is compared to an estimated cost in an average collection volume

based on the maximum volumes in relation to body weight applied in the United States.(92) According to the regulations of the FDA, the maximum volume per collection is 690 ml, anticoagulant solution included, for individuals weighing between 50 kg and 67 kg, 825 ml for individuals between 68 kg and 80 kg, and 880 ml for persons weighing more than 80 kg.

Data on body weight of Swedish plasma donors have been collected from the blood establishment at the Karolinska Hospital and from the blood establishment at the hospital in Härnösand.(85) In the sample from the Karolinska Hospital, 18% of the donors weighed between 50 kg and 67 kg, 28% weighed between 68 kg and 80 kg, and 54% weighed more than 80 kg. In Härnösand, 30% of the donors weighed between 50 kg and 67 kg, 37% weighed between 68 kg and 80 kg, and 33% weighed more than 80 kg. Hence, the data from the Karolinska Hospital showed a larger share of donors in the heaviest weight group.

Using the weight distribution from the Karolinska Hospital, the estimated average collection volume for the blood establishments is 830 ml, anticoagulants included. Using the weight distribution reported by Härnösand, the corresponding collection volume is 803 ml. The actual average volume reported by the 19 blood establishments responding to the questionnaire was 604 ml.

5.5.2 Cost at Different Collection Volumes

The average cost of production and a 95% confidence interval have been calculated, based partly on the real cost data and collection volumes reported by the 19 units, and based partly on estimates using the two alternatives described above at volumes of 803 ml and 830 ml, respectively (Diagram 5:3).

Diagram 5:3. Mean value and 95% confidence interval for cost per kg source plasma at a volume of 604 ml compared to a volume of 803 ml and 830 ml per donation, respectively, at a constant number of collections and constant quantity of kg, respectively. 19 Swedish blood establishments. Year 1996.

At approximately 600 ml of source plasma per collection, the average cost was 1028 SEK per kg. A 95% confidence interval is between 962 SEK and 1093 SEK per kg.

Based on the alternative *unchanged total quantity of plasma* and approximately 800 ml on average per collection, the average cost is 876 SEK (k1 in diagram 5:3). A 95% confidence interval is

between 816 SEK and 935 SEK per kg. At 830 ml per collection, the average cost is 860 SEK (k2) and the confidence interval is between 801 SEK and 920 SEK.

Based on the alternative *unchanged number of collections* and 800 ml of source plasma per collection, the average cost is 772 SEK (T1 in diagram 5:3). A 95% confidence interval is between 730 SEK and 813 SEK per kg. In 830 ml of source plasma per collection, the average cost is 746 SEK (t2) and the corresponding confidence interval is between 706 SEK and 786 SEK.

The two production costs calculated at 800 ml and 830 ml, respectively, are statistically significantly lower than the actual average cost at 600 ml. In the example based on an unchanged total quantity of plasma, the lower cost of production per kg is a result of the lower total variable costs per kg. In the example based on an unchanged number of collections, the lower cost of production per kg of source plasma is due to the total variable cost and the total fixed cost being lower per kg.

The possibility to increase the collection volume depends on whether this is acceptable to donors. In reality, it is also unlikely that an average collection volume of 800 or 830 ml of source plasma (anticoagulant solution included) can be achieved at the blood establishments. Collection volumes per weight class are the maximum allowed on one occasion. Due to differences in the individual donors and other factors such as spoilage, etc, the average volume per collection will probably fall below the stated maximum.

An increase in volume may cause problems in maintaining the number of collections. Due to physiological differences, it may be faster to collect from a female donor than a male. Since men normally have a greater body weight, they constitute most of the donors weighing over 80 kg and can give a maximum of 880 ml. The time required per session for some males may need to be extended significantly to obtain 880 ml. Apart from greater inconvenience to the donor, the increased time may make it more difficult to maintain the same number of collections as previously without adding resources, e.g. staff.

5.5.3 Possible Cost Reduction at Increased Collection Volumes

If the real costs of production per kg of source plasma at the respective blood establishments are compared to the estimated costs at the alternative volumes described in the model above, one can surmise the potential achievable cost decrease per kg.

In the example of a *constant total quantity of plasma*, the 19 blood establishments achieve an average cost decrease per kg plasma of nearly 15% at 803 ml of plasma per collection, and slightly over 16% at 830 ml. A constant quantity of plasma, however, means that the total number of collections decreases between 24% and 26%. Such a reduction in activity would probably cause a change in several of the cost items that are assumed to remain unchanged in the model.

In the second example using a *constant number of plasma collections* in the blood establishments, averaging 800 ml and 830 ml plasma per collection, respectively, the cost decrease is between 24% and 27% per kg. In this calculation, the total quantity of collected plasma increases between 34% and 36%. Considering that the delivery of plasma from the blood establishments in 1996 exceeded the estimated need for national self-sufficiency, an increase of this magnitude would yield a substantial excess of source plasma. From an EU perspective, aiming at European self-sufficiency, this situation could make it possible to export the excess to other countries in Europe. An increased quantity of source plasma at competitively better prices for the domestic pharmaceutical industry might also contribute to large-scale advantages in the production of plasma derived pharmaceuticals, which can strengthen the conditions for continued national self-sufficiency.

5.6 Cost Coverage by Changes in Occupancy Rates and Volume

In the prevailing situation in the Swedish market, with free competition between domestic plasma and imported plasma, the low price of American plasma encourages the pharmaceutical industry to press for lower purchasing prices in negotiating with the blood establishments on price and quantity. Hence, it is worthwhile exploring the blood establishments' possibilities to adjust their activities to different price levels. Due to variations among the blood establishments in the cost per kg plasma, there are also variations in their possibilities to maintain or achieve a balance between costs and revenue if the price for source plasma decreases.

5.6.1 Occupancy Rate

Utilization of capacity, based on occupancy rates in collecting source plasma, has been estimated from questionnaire data on the number of *actual* collections in relation to number of *possible* collections. Occupancy rates calculated in this manner varied between 61.2% and 97.9%, with a median of 79.2%.

The median value seems to be relatively high, which may be due to the fact that some blood establishments have problems in estimating the number of possible collections which could have been performed during 1996. The number of possible collections may have been related to the actual number of staff available to handle plasma collection in the blood establishment during the year.

5.6.2 Significance of Capacity Utilization

In order to observe ways of reducing the production costs for source plasma, some estimates focused on the impact of increasing utilization by increasing the occupancy rates. Calculations are based on a short-term situation and constant fixed costs. Given

otherwise unchanged unit prices and collection volumes, the calculations show that an increase in the occupancy rate of 5 *percentage points* above the original level results in a decrease in the production cost per kg plasma between 2 and 3 *percent*. An increase in the occupancy rate by 10 *percentage points* yields a decrease in the cost per kg between 3 and 5 *percent*.

Another area of potential savings concerns the cost differences involved in collecting more from already known donors as compared to recruiting new donors. Personnel resources and marketing expenditures are required to recruit potential donors. Prior to accepting an individual as a plasma donor, he/she must undergo a series of checks to minimize the potential risk of infection, etc. Such controls, e.g. interviews and blood samples, require resources. If more donations can be collected from known donors, some of the new recruitment costs can be avoided, yielding a lower cost per kg of plasma.

The above examples can be compared to the results from previous estimates of the consequences of increasing the volume per plasma collection. The opportunities to favorably influence costs seem to be substantially greater by changing the volume per collection session as compared to changing the occupancy rate. However, blood establishments should consider both of these possibilities to achieve satisfactory results in plasmapheresis activities. From a business standpoint, however, the conditions for this are quite different among the blood establishments, as illustrated in the three examples below.

5.6.3 Three Scenarios

Three groups of blood establishments can be distinguished based on their relative cost situation. One group consists of the blood establishments which have the lowest costs per kg of source plasma, with a relatively favorable cost situation in relation to potential revenue. The second group has somewhat higher costs for plasma and hence a less favorable cost situation. The third group consists

of the units having the highest costs and are in an unfavorable cost situation.

Three blood establishments, representative of the cost situation in their respective groups, have been selected and are described below. The cases are based on a simple model where the total fixed cost is assumed to be constant across the scope of activity. Fixed costs include personnel, facilities, equipment, and other costs. Variable costs include material, laboratory tests, and donor compensation, including costs for refreshments.

Case 1 – favorable cost situation

The blood establishment performed slightly over 19 000 plasmapheresis collections during 1996, yielding nearly 12 000 kg of plasma. The average volume per collection session was 620 ml, anticoagulant solution included. The occupancy rate was 77%.

Diagram 5:4 shows the total revenue and costs in million SEK on the vertical axis and total quantity of source plasma in kg on the horizontal axis. The fixed cost (FC) was somewhat over four million SEK. The variable cost (VC) in collection of 620 ml per session is indicated by the line VC 620 ml, and the corresponding cost for 830 ml per session by the line VC 830 ml. The blood bank's situation in 1996 is marked by an X on the line VC 620 ml. The diagram also includes two lines which show the total revenue at different prices and quantities of plasma. One line, 1050 SEK/kg, shows the revenue level at the price level in 1996. The second line shows the revenue level at a price of 950 SEK/kg source plasma. Different occupancy rates, based on activity in 1996, are marked with vertical lines (50%-80%).

Diagram 5:4. Costs and revenue for source plasma at a blood establishment. Comparison among different occupancy rates (50-80%), different costs at volumes of 620 ml and 830 ml of plasma per donation, and different prices (950-1050 SEK/kg), 1996.

In this example, the revenue line for 1050 SEK/kg is well above the cost line VC 620 ml for the quantity of 12 000 kg of plasma per year. Also, the revenue line for 950 SEK/kg is above the cost line for 620 ml. A change in price of plasma to 950 SEK yields lower profits at the same quantity, but the result is still positive. A decrease in the variable costs per kg by increased volume per collection session would increase profits for the blood establishment. A downward shift then takes place so that the

variable costs fall between VC 620 ml and VC 830 ml. Profits would also increase if the occupancy rate could be increased. An increased occupancy rate via a greater number of collections means greater quantity and a shift to the right along the cost line VC 620 ml.

Case 2 – a less favorable cost situation

This blood establishment performed approximately 5600 collections in 1996, yielding somewhat over 3300 kg of source plasma. The average volume per collection session was 600 ml. The occupancy rate was 80%. (Diagram 5:5). The total fixed costs, FC, amount to nearly 1.3 million SEK. There was some surplus in 1996, since the revenue line for 1050 SEK/kg falls above the cost line VC 600 ml at the quantity 3300 kg (marked by an X in the diagram). A change in the price per kg of plasma to 950 SEK resulted, however, in a loss to the blood establishment as illustrated by the revenue line 950 SEK/kg falling below the cost line VC 600 ml at the given quantity.

To achieve a balance between costs and revenue, the blood establishment can try to increase the plasma volume per collection session. The costs decrease, which causes a shift downward toward the line VC 830 ml. If, on the other hand, the volume per collection session remains unchanged at 600 ml, the goal to achieve a balance between costs and revenue would involve a need to change the quantity, which is equivalent to an increase in the occupancy rate from 80% to more than 90% (the point where the lines 950 SEK/kg and VC 600 ml intersect).

Diagram 5:5. Costs and revenue for source plasma at a blood establishment. Comparison among different occupancy rates (50-100%), different costs at volumes of 600 ml and 830 ml of plasma per donation, and different prices (950-1050 SEK/kg), 1996.

The collected quantity of plasma would increase from approximately 3300 kg to 3900 kg since the number of actual collections increases from approximately 5600 to 6500. In reality, it is probably impossible to achieve this higher level of utilization without changing the fixed costs, e.g. personnel costs. For this blood establishment to achieve financial balance, an increase in the volume per collection session would probably be required.

Case 3 – an unfavorable cost situation

In this blood establishment, approximately 10 000 collections were performed, which yielded 6200 kg of source plasma. Average volume per collection session was 620 ml and occupancy rate was 70% (Diagram 5:6).

Diagram 5:6. Costs and revenue for source plasma at a blood establishment. Comparison among different occupancy rates (50-100%), different costs at volumes of 620 ml and 830 ml of plasma per donation, and different prices (950-1050 SEK/kg), 1996.

The total fixed costs amount to approximately 4 million SEK. The position of the blood establishment is marked by an X. At a quantity of 6200 kg, the blood establishment realizes a loss from plasma services. Both revenue lines are situated below the cost line VC 620 ml at this quantity. A price of 1050 SEK per kg source plasma would be potentially profitable if both the volume per collection session and the occupancy rate would increase. If the price decreases to 950 SEK/kg, it is not possible to balance costs and revenues if the average volume plasma per session, 620 ml, is maintained – not even at an occupancy rate of 100%.

A large increase in the average collection volume, with a concurrent increase in the occupancy rate to nearly 90%, is the only possible way to achieve balance if the other variables are constant. This would mean increasing the number of collections from approximately 10 000 to 13 000, which would be difficult to achieve within the given framework.

The case describes the acute situation in which blood establishments with the highest costs find themselves. The example shows these blood establishments need to thoroughly review all plasmapheresis activities, their organizations, personnel costs, etc.

5.7 Attempts to Economize: Three European Examples

There are no empirical studies available to illustrate the economic impact of organizing blood and plasma services in different ways. However, theoretical examples can be discussed concerning the advantages and disadvantages of large-scale production.

Grönqvist et al have reported on some of the literature addressing hospital experience with large-scale production.(93) Large-scale production offers the opportunity to spread fixed costs across larger production volumes. Fixed costs include, e.g. costs for equipment or basic staffing. Large production units provide greater possibilities to use specialized resources, e.g. equipment or manpower. In larger units, it costs relatively less to maintain a

given level of preparedness beyond ”normal” activity. Larger purchasing volumes make it possible to negotiate better prices.

Large-scale production may also have disadvantages, such as more unwieldy organizations and higher costs for coordination and control. The potential advantages of large-scale production must be weighed against the increased cost of transport and possibly lower accessibility resulting from the consolidation of activity.

The following presentation aims to describe the structure of systems that intend to guarantee national self-sufficiency. Furthermore, it shows that a body of experience is available to draw upon from other countries which have extensively reorganized blood services. Hence, the following examples are not intended to show that centralized national services are necessarily better than more decentralized services, as is the case in Sweden. Plasma activities in the three countries described below are not as extensive as those in Sweden. Most of the collected plasma consists of recovered plasma from blood donation.

5.7.1 Finland

In Finland, blood transfusion activities are structured as an independent national organization under the Red Cross.(94) Collection is based on voluntary, uncompensated blood donations. Blood transfusion services are available throughout Finland, with 21 centres and mobile units. The national establishment is located in Helsinki, which is the site for administration, all laboratory testing, and purchasing of material, collection kits, etc. There are four regional centres: the university cities of Kuopio, Uleåborg, Tammerfors, and Åbo. The blood collected in 16 local centres is brought to these centres to be separated into different blood components. The local blood establishments only collect blood, which is transported daily to the closest regional establishment or to Helsinki. Approximately 45% of the donations take place in two mobile units, one in Helsinki and one in the rural area.

Approximately 80% of the total staffing of approximately 600 persons are located in Helsinki. The personnel at the establishment

in Helsinki, at the mobile unit in Helsinki, and the mobile unit in the rural area belong to a common ”pool”. The number of persons who can work in the mobile units is determined based on the expected number of blood donations.

Plasma collection is relatively rare in Finland and only occurs in Helsinki, approximately 1000 collections annually. The only domestic fractionation industry is in Helsinki, with a capacity of approximately 120 tons of plasma per year. The blood transfusion service has an estimated cost for plasma – a mixture of component and plasmapheresis plasma – equivalent to approximately 600 SEK per liter.

Laboratory activities are located in Helsinki to achieve economies of scale. All samples are transported to Helsinki during the night and analyzed the following day. Blood collected by the local centres and by the rural mobile unit is transported to the nearest regional establishment at night. The cost for contracted transportation services amounts to 4 million FIM per year. The cost for transportation provided by the blood transfusion service itself amounts to approximately 2 million FIM per year (depreciation on vehicles is not included in this sum).(95,96)

5.7.2 France

In France, blood services were reorganized to ensure the quality of collected blood and minimize the risk for infection in blood transfusion. In 1993, a law concerning safety in blood transfusion was adopted. The law formed the foundation for a plan to reorganize blood services nationally. The goals established via the reform focused on maintaining existing blood establishments and places of distribution, but limiting the number of manufacturing and control activities in producing blood components. Blood services are now guided by regulations stipulating professional management. Blood donation is strictly voluntary and based on complete anonymity, and services are organized on a non-profit basis.

Previously, transfusion activities were offered in approximately 180 hospitals with no official regulatory control. Transfusion ac-

tivities were split among different administrative units and under 7 different laws.

A new, national public organization, Agence Francaise du Sang (AFS), was created to assure the standard of blood transfusion activities. The organization is charged with the general administration and financing of services, and supporting research in transfusion medicine. AFS also supervises compliance with regulations, and studies the cost and quality of services.

The only fractionation company in France is located within AFS. There are 43 administrative blood transfusion centres which have a monopoly on transfusion services and plasma collection. Blood transfusion, blood and plasma collection, etc take place at 165 sites. In 1994, over 9000 people were employed, corresponding to 7855 full-time employees.(97)

The agency, which is under the Ministry of Health, had 73 employees in 1995. Each month, the manager of AFS reports to the Minister. The annual budget is frozen at 100 million French Francs (FRF). Financing is shared between the state and the national health insurance. 40 million FRF of the AFS budget goes to financing the activities at INTS, l'Institut National de la Transfusion Sanguine, which has a total budget of 70 million FRF. INTS supports blood transfusion centres with special services in immunology and virology, etc, and manages research projects and education of personnel.

The AFS also administers the budget of FORTS, Fonds d'Orientation de la Transfusion Sanguine. The budget of FORTS is 110 million FRF, financed by grants based on a percentage of revenues from the sale of blood products from all blood transfusion centres. The fund is to support and facilitate the adaptation of blood services to the new safety and quality regulations. FORTS supports educational programs for staff, investments in new construction, renovation, and safer, more efficient equipment, and also provides research grants.

5.7.3 Great Britain

The reorganization of blood services in Great Britain has taken place during a time of economic cutbacks in medical care. Large sums have been invested during the reorganization phase, but the investment is expected to pay off as the new organization generates savings in the delivery of services. An important aspect of the reorganization involves following up on the initiatives to improve services and on any new problems.

Until April 1994, blood services were managed by individual Regional Health Authorities. Lack of coordination among the regions meant that national access to blood was not assured. Differences in local practices concerning the manufacture of blood products made it difficult to establish common national quality standards, which, in turn, made it difficult to use a product in more than one region. Differences in the selection criteria for donors meant that some individuals were unnecessarily excluded from donating blood. Excessively high capacity in production and testing, and a lack of coordination in purchasing equipment and supplies also resulted in inefficiencies.

To solve these problems, a special health authority was established in the NHS, National Blood Authority (NBA), in 1994. Blood services were reorganized into several regional transfusion centres. Previously, blood collection had taken place in hospitals. Later, special collection units were established to complement those already existing. Blood is transported to regional centres for testing. The goal is to decrease (from 15 to 10) the number of units offering testing and further refinement of blood. The regional transfusion centres now supply approximately 380 hospitals with blood when required. The aim of reorganization is to decrease hospital costs for blood and blood products. Administration was divided into 3 regional zones for England. The number of personnel was estimated to decrease by 7% over a 3-year period, which corresponds to approximately 300 positions from 4000 full time equivalents.

The expected economic outcome after reorganization has been described in the following manner. An estimated total net savings of approximately 3 million pounds can be achieved by consolidating

the administration of blood donors into the three zone centres. Improved planning in the size of staffing and other resources will bring these into better balance with the number of donors. An increased number of local collection teams will decrease travel costs for personnel. Introduction of computer-based administration will decrease waiting times for donors and simplify administrative routines. Improved logistics will more than offset the increased cost of transportation which will result from the reduction in the number of testing and production plants.

Large sums are being invested in a national, uniform information system to replace the different and sometimes outmoded systems used in the different regions. During the period, investments will be made to improve research and development. New centres for Research and Development are planned, which will, e.g. conduct research on the relationship between the use of blood and clinical outcomes. Investments are being made to increase the support to hospitals with services in transfusion medicine. Better education and new work methods are expected to lead to the best possible practices in transfusion medicine.(98)

5.8 Concluding Remarks

Many blood establishments in Sweden have difficulties in specifying the costs for plasma services. Some units are organizationally situated under hospital laboratory services, and blood and plasma activities are not distinguished from lab services in hospital cost accounting. Another problem related to cost allocation is the inability to specifically attribute certain types of cost to plasma services. Common examples include personnel costs, costs for facilities, costs for equipment, and shared operational costs of the hospital. Local practices vary widely, making economic comparisons of plasma services among blood establishments difficult.

In blood establishments that collect plasma, these activities normally represent a substantial part of the blood bank’s overall

activities. The total revenue from sales of source plasma, which is offset by approximately equally as large costs, averages 21% of the total cost of the blood establishment, i.e. approximately one fifth. If the total income which blood establishments receive for recovered plasma is added, often more than 10% in relation to the total cost of the centre, it is apparent that the activities of the blood establishment and the resources required depend heavily on the revenue from plasma sales.

Pharmaceutical companies in the Swedish market pay different prices for source plasma. The largest purchaser, Pharmacia & Upjohn, pays approximately 950 SEK per kg, while Baxter (Immuno) presently offers a somewhat lower price (VAT excluded) to the blood establishments. Currently, there appears to be different practices in accounting for VAT in the plasma trade. National Swedish Tax Board regulations leave room for different interpretations. Hence, the regulations should be revised so as to avoid local deviations from a uniform, national interpretation.

The *average cost* in the blood establishments for one kg of source plasma was approximately 1000 SEK in 1996. Cost levels among blood establishments vary widely, from less than 800 SEK to more than 1300 SEK per kg.

Personnel costs represent one of the larger cost items, and there are relatively large differences among the centres concerning this item. It appears that the blood establishments with the higher total costs per kg have relatively high costs for personnel and/or laboratory tests. In some cases, these blood establishments also have relatively high ”other” costs, i.e. various shared costs in the hospital, etc. Centres with a high total cost tend to have somewhat higher material costs than centres with a low total cost.

A factor which may partly underlie the differences in production costs per kg of source plasma is that blood establishments reporting relatively low costs generally collected a somewhat larger quantity of plasma per donor session than centres reporting higher costs. However, volume differences were small.

Increasing the collection volume depends on donor acceptance. Changing to the collection volumes used in the United States would

increase the potential for productivity gains. The opportunity to influence costs in a favorable direction seems to be substantially improved by changing the volume per collection session compared to changing the occupancy rate. However, blood establishments should consider both possibilities as they aim to hold their unit prices down and achieve satisfactory results in plasma services. From a business viewpoint, however, this varies widely among the different blood establishments. The centres with the highest costs per kg of source plasma cannot cover their costs for these services given the current market price. There is an urgent need for a thorough review of all plasma activities in these blood establishments, their organization, personnel costs, etc.

An increased quantity of source plasma at competitively better prices in the domestic pharmaceutical industry might contribute to economies of scale in producing drugs based on plasma, which can strengthen the conditions for continued national self-sufficiency.

There is no empirical foundation describing the cost-effectiveness of alternative organizational solutions. Positive experiences as well as problems can be found in nations which have restructured their blood services into nationally centralized organizations to help ensure national self-sufficiency of blood and plasma.

6 Considerations and Recommendations

The following chapter presents several measures which the Working Group suggests should be taken to ensure Swedish self-sufficiency in the future and work closer toward the goal of European self-sufficiency in plasma and plasma products. By definition, self-sufficiency means that the supply of source plasma is in balance with the demand for plasma products manufactured from source plasma. The aim of the Working Group has been to analyze and review factors and circumstances influencing both supply and demand.

It is important to note that membership in EU means that plasma for fractionation is a commodity which should be permitted to move freely across borders between member countries. Hence, Swedish issues cannot be analyzed or addressed in isolation, but must be viewed in a broader European perspective.

Another issue is that self-sufficiency problems cannot be isolated from issues concerning the safety of blood and blood products. Self-sufficiency within the European Union requires trust among the member states concerning the quality and safety of products manufactured in countries other than one's own. Such trust can be created only by harmonizing regulations and routines related to the safety of plasma and plasma products. The Working Group's views concerning these issues are presented in section 6.1.

The supply of blood plasma depends on, e.g. access to plasma donors and allowed collection volumes. For Sweden, it is important to review the allowed collection volumes and collection frequencies to determine whether productivity and competitiveness of plasma

services can be enhanced, without risk to the donors, by increasing the collection volumes, thereby assuring an adequate supply of source plasma. Suggestions concerning the scientific review of alternative collection volumes are presented in section 6.2. Poor access to plasma donors is a problem in several European countries. Hence, the issue of compensation for plasma donation – and the ethical problems associated with compensation – are discussed in section 6.3.

Section 6.4 discusses some of the national issues concerning the production of plasma and plasma products. This includes the need to review the structure, organization, and cost-effectiveness of services. Section 6.5 addresses the issue of regulating the national responsibility for plasma supplies. Since the donation and delivery of plasma to the pharmaceutical industry appears to have little impact on Swedish emergency preparedness planning, these issues are not addressed.(99)

Utilization of the end products manufactured from source plasma varies considerably among EU nations and among different areas in Sweden. Demand is largely determined by local and regional treatment traditions and routines. In section 6.6, the Working Group offers several suggestions concerning the scientific review of indications for the use of plasma products.

Section 6.7 addresses issues affecting the profitability and future perspective of the fractionation industry.

New, improved forms for international collaboration concerning blood and plasma issues are suggested in section 6.8. The association between collaborative international efforts and the regulatory work of national Swedish authorities is also discussed.

6.1 Importance of Harmonizing Regulations on Plasma Safety

To achieve European self-sufficiency in plasma and plasma products, a sense of confidence must exist among the member states concerning the quality and safety of products manufactured in

countries other than one's own. Although small, there is always a risk in using plasma derivatives. The unforeseen spread of HIV/AIDS during the 1980s resulted in extensive human suffering and caused political turbulence in several countries. Similar problems may be encountered in the future, caused by yet unknown viruses or other infectious agents. With free mobility for blood products within EU, it is necessary to work toward a common, harmonized view on the safety standards to be applied in EU.

Unfortunately, conditions in Europe remain far from uniform, even though the regulatory process for approval and control of plasma products is supposed to be the same within EU. Until 1992, plasma drugs were under national control in several of the member states, and the national plasma fractionation companies held a strong, monopoly-like position in their respective home countries. Furthermore, in most member states, the use of blood components for transfusion purposes has been considered a part of nationally regulated medical services. Blood components for transfusion purposes remain under strict national control, while plasma derivatives of European origin are supposed comply with the regulations established by EU. However, certain standards of a national character may still play a role in some member states.

The Working Group considers the recommendations on selecting donors and testing donated blood (upon which the EU health ministers recently achieved political agreement) to be an important step in the European harmonization process. In the long run, the goal should be that all plasma products – whether produced within EU or imported – adhere to standards specified by the European Commission, the Council of Ministers, the central pharmaceutical authorities within EU, the European Agency for the Evaluation of Medicinal Products (EMEA), and the European Pharmacopoeia. Only then, can safety be assured and fair competition exist between imported products and those produced within EU.

6.2 Testing Regulations for Plasma Collection Volumes

Because the use of plasma products has gradually increased and reached a level which cannot be met by recovered plasma, the issue of self-sufficiency has increasingly focused on the access to and supply of source plasma. A review of available cost and price information confirms what was previously reported by representatives of plasma centres and the plasma industry, that the price for European source plasma is around 50% higher than the price for equivalent plasma from the United States.

Production costs for source plasma are influenced by several variables. Factors which play an important role in this context include the number of staff, use of test kits, utilization as measured by occupancy rates in the collection units, and the amount of plasma collected per donation. In general, it is difficult to reduce the collection costs for blood plasma by lowering the fixed costs in the plasma centres. One way of influencing the cost in Sweden would be to increase the occupancy rates. Another would be to purchase larger quantities of test materials to negotiate more favorable prices. Such measures require a systematic review of the organization and economy of the units. This is discussed further in section 6.4.

From a fundamental and economic standpoint, it is important to review the current differences between American and European regulations for plasma collection and take relevant measures to neutralize competition. As previously stated, the Council of Europe has, for many years, recommended collecting a maximum of 650 ml of plasma during one session and a maximum of 15 l of plasma per donor and year. The Swedish regulations comply with the recommendations from the Council of Europe. In the United States, however, up to 800 ml can be collected per session, and between 80 l and 90 l can be collected per year, depending on the body weight of the donor. In practice, the differences in collection volumes and intervals mean that more donors are interviewed, tested, and collected in Europe than in the United States to collect the same

amount of source plasma. This obviously results in a higher total cost per kg for plasma collected in Europe.

To avoid this distorted competitive situation, several solutions are feasible. The long-term goal should be that all plasma products marketed and used in Europe should be manufactured from plasma collected in accordance with uniform regulations based on science and reliable clinical practice. However, this investigation indicates that, due to a lack of scientific studies, current knowledge is vague as regards the health consequences of alternative collection volumes. Practices in both Europe and the United States seem to rest on a fragile scientific foundation. Progress has also been influenced by limitations associated with the apheresis technique itself, which earlier offered limited possibilities to individually adjust collection volumes, e.g. according to donor weight and gender. Today, however, the technical opportunities are considerably better.

Therefore, the Working Group considers it essential to, as soon as possible, conduct a Pan-European, prospective multicenter study on the consequences to donor health of alternative, more individually adapted, collection routines. Apart from the health effects, it is also essential to study the costs of different collection programs. The purpose of these randomized trials would be to analyze whether collection volumes can be increased without negatively affecting the health of donors. The test subjects – plasma donors who have given informed consent to participate in the study – are randomized to three or four alternative collection schedules and followed up concerning essential plasma parameters and general measures of health status. Another purpose would be to illustrate the association between collection volumes and the total costs for source plasma, requiring detailed cost analysis of a stratified sample of plasma centres.

Since the issues are of major Pan-European interest, the Working Group suggested in its background document to the Council of Europe of Health Ministers in June 1997 that such a study should receive financial support from the European Commission. The lack of scientific evidence was addressed in the new

EU recommendation, and the European Commission DGV intends to support a study of alternative collection schedules.

In Sweden, it is important that the Swedish Medical Research Council actively support Swedish participation in the study.

6.3 Ethics and Unpaid Plasma Donation

Blood donation has always been surrounded by certain ethical considerations. Giving blood has been considered an altruistic gesture, performed to help fellow humans in need. From an ethical perspective, it seems obvious that donating a body part, an organ, or blood should be a gesture of solidarity and hence should not be reimbursed with money or other payment. As long as the demand for blood was limited, and collected blood was transferred directly to another person, this way of viewing the problem as a purely ethical consideration could be maintained, and there appeared to be no reason to discuss any other arrangement.

When collected blood, or plasma, is used as source plasma to manufacture different products, the situation becomes different. In such cases, it does not seem unreasonable to compensate the individual donor for the discomfort and time associated with the procedure. It is not unlikely that there will be a greater call for compensation in plasma donation if European plasma centres intensify their collection schedules to increase their production and effectiveness.

The basis for selecting donors has always been that the donor should be healthy – so as not to expose the donor to risk and to assure a high quality of blood to the recipient. This requirement became more stringent after the transfer of blood and blood products was shown to carry a risk for infection. Since certain life styles may increase these risks, it has been considered important to avoid attracting at-risk individuals through monetary compensation.(100) The extent to which relatively modest compensation would actually attract this category of donor – and whether these donors would actually create a higher risk for the spread of infection through end

products in a modern plasma industry with its extensive checks of collected blood and plasma – has not been investigated.

Sweden is among the countries in Europe that have succeeded in reaching the goal of self-sufficiency. Other countries, such as Germany and Spain, have had problems in recruiting an adequate number of donors. With the increasing demand for plasma to manufacture plasma drugs, organizations that manage plasma collection in several European countries have bypassed the regulation of ”non-remunerated donation” by reimbursing the donor with one half to two days of time off from work, different types of points (which can be exchanged for certain goods), or other forms of non-monetary compensation. This method of bypassing the regulation can be questioned from an ethical standpoint and illustrates a weakness in the agreement on ”non-remunerated donation”.

In the United States, there are no equivalent restrictions, and plasma services do not seem to experience any disadvantages from paying a reasonable compensation to donors.(101) The ethics of donating plasma have also been attacked in the United States, but from a different angle. There, it is emphasized that not paying donors is unethical since the plasma will be used in industrial activities where companies buy the plasma for raw material in commercial production. This is indeed the case even in Europe.

In the light of the discussion above, the Working Group wishes to emphasize that it is not self-evident that all blood and plasma donation should be ”non-remunerated donation”. Actually, it is time to openly define the term ”non-remuneration”. Existing variations in compensation practices could be used as a point of departure to study the possible association between the level of compensation and plasma safety. It is also possible that some European countries, under controlled circumstances, are willing to prospectively study the effects of different compensation practices. Such research initiatives should be of interest to the Council of Europe which, for many years, has monitored ethical issues concerning blood activities.

6.4 Cost-effectiveness of Swedish Plasma Services

In 1996, the average production cost for one kg of source plasma in the blood establishments was 1028 SEK. Costs vary widely among blood establishments, from barely 800 SEK to more than 1300 SEK per kg. The pharmaceutical companies in the Swedish market pay different prices for source plasma. The largest purchaser, Pharmacia & Upjohn, pays approximately 950 SEK per kg, while Baxter (Immuno) presently offers a somewhat lower price (VAT excluded) to the blood establishments.

An economic issue, influencing the profitability of plasmapheresis services, relates to interpretation of the Swedish VAT legislation concerning county council sales of source plasma. Sales of recovered plasma from whole blood collection is viewed as disposing of a byproduct in an otherwise tax-free health service, hence sales are exempt from VAT. Plasmapheresis plasma can be either equaled to recovered plasma or be defined as a product created via a special process that is a nonessential part of the health service. In the latter case, apheresis activities can be viewed as sales of a primary product, subjected to VAT. Discussions with representatives from plasma centres and the plasma industry indicate that the interpretation of the regulations is unclear. The regulations of the National Swedish Tax Board should therefore be reviewed so as to avoid local deviations from a uniform, national interpretation.

From an international perspective, plasma activities in Sweden are characterized by many relatively small collection units. This is a disadvantage, e.g. in purchasing situations, where small volumes may result in higher unit prices for test kits, etc. There have been discussions on consolidation in Sweden. Consolidation may, however, create problems related to competency and efficient supervision of the remaining transfusion activities.

To increase safety and cost-effectiveness, several European countries have centralized their blood and plasma activities. There is no empirical foundation available, describing the cost-effective-

ness of alternative organizational solutions. Both positive experiences and problems can be observed in countries where blood services have been restructured into a nationally centralized organization. Given the complexity of the issues, the Working Group proposes a national review to address structure, organization, and cost-effectiveness. Obvious collaborators in such a review would be the Federation of Swedish County Councils, the National Swedish Board of Health and Welfare, the Medical Products Agency, and the Spri. Since experience from abroad indicates that national reorganization may take several years, it is essential to begin work immediately. As a result of discussions in the Working Group, the Federation of Swedish County Councils has already initiated planning for such a review.

6.5 Regulation of National Responsibility for Plasma Supply

Although more than 90% of current plasma collection takes place under the management of the health service, no regulations require the county councils to collect plasma that will not be used for direct transfusion to patients. If the collection of source plasma for fractionation does not cover the costs, there is a risk that local decisions will be made to discontinue this service even though Sweden is committed to the goal of European self-sufficiency.

Since 1985, the National Swedish Board of Health and Welfare has been assigned by the government to monitor progress toward increased self-sufficiency in blood and blood plasma. This responsibility does not offer any real opportunity to manage apheresis activities. Current problems were not an issue in the mid 1980s, and plasmapheresis activities did not develop on a larger scale until the latter 1980s. The goal of European self-sufficiency as specified in EU directive 1989/381 did not become binding until Sweden entered EU. The role of the Swedish authorities is complicated since the National Swedish Board of Health and Welfare supervises

traditional transfusion activities, while the Medical Products Agency supervises the manufacture of blood components used as source plasma for pharmaceuticals.

In the light of the events of the past decade, national responsibilities need to be clarified. It must be specified which authority or authorities are responsible for Sweden's contribution, as a member state of EU, toward self-sufficiency, and which incentives or sanctions can be used in working toward this goal. The Working Group suggests that the National Swedish Board of Health and Welfare and the Medical Products Agency be charged with reviewing Swedish legislation to determine how national responsibilities for plasma supply can be best regulated.

A central issue in this context is whether the collection of plasma for fractionation can – analogous to blood collection for transfusion – be defined as part of the county councils' responsibilities. Collection of source plasma for pharmaceutical manufacture is an activity of a basically different character than local transfusion activities. There is, however, a strong practical connection between the two. The assessment must also consider that the end products manufactured from source plasma are an integral part of the treatment arsenal required to meet the population's need for medical care.

If collection of source plasma for pharmaceutical manufacturing is defined as part of the county councils' responsibilities, the aim should be optimal national coordination. Increased cooperation between the county councils may be required to protect the quality, safety, and cost-effectiveness of plasma services.

6.6 Evidence-based Medicine as a Foundation for Using Plasma Products

Utilization of end products manufactured from source plasma – mainly coagulation factor VIII, albumin, and immunoglobulins – varies among EU nations and among areas in Sweden due to

differences in the occurrence of certain diseases and clinical practice variations in treating comparable patients. Although issues related to the optimal use of plasma and plasma products have been noted at a European level, they had relatively low priority.

Medical practice variations are often due to local treatment traditions. Previous medical care research has shown that the weaker the scientific evidence for a certain treatment, the greater the variations in clinical practice. It is the judgment of the Working Group that the scientific foundation for clinical application of plasma and plasma products needs to be focused on and enhanced through systematic reports of existing knowledge and by scientifically-designed primary studies of the benefit, safety, and cost-effectiveness of these products. The need for research contributions is accentuated by the introduction of new, genetically engineered alternatives to plasma derived products. Other factors concerning the use of various blood components may also affect future developments.

On the initiative of the Working Group, the Swedish Medical Research Council has appointed a group to prepare a state-of-the-art conference on the use of plasma and plasma products. In the long run, this initiative may lead to new Pan-European decisions concerning on indications for some plasma products. In European collaboration on self-sufficiency problems, Sweden should contribute by focusing greater attention on issues related to the optimum use of plasma products.

To enhance knowledge about safety in blood and plasma activities, international registration of side effects and complications in transfusion of blood and blood components is being planned within the scope of the so-called ISPOT study (International Study of PeriOperative Transfusion). In Europe, e.g. the French blood institute, Agence Francaise du Sang, AFS has presented initiatives concerning a common hemovigilance system. The Working Group holds the opinion that it would be valuable if Sweden contributed actively to the international effort toward systematic registration and reporting of side effects and complications in transfusion activities. Apart from the National Swedish Board of Health and

Welfare, the Medical Products Agency can offer valuable support given its extensive experience in reporting pharmaceutical side effects.

Computerization of the blood activities in Sweden offers greater opportunities to effectively follow up on the volume, cost-effectiveness, and safety of services. The Swedish Society for Transfusion Medicine has developed a relatively well functioning registry of complications, but possibilities for systematic analysis and reporting of the information have been somewhat lacking. It is remarkable that registration of complications in apheresis services (previously a Dagmar-project) lacks financing. Information on risks and complications are also collected in the Risk Data Base of the National Swedish Board of Health and Welfare and in the computer systems of the malpractice insurance authority and the health services disciplinary board. The Working Group considers it essential to allocate resources so that existing data can be compiled and the results can be continuously reported to the blood and plasma services and the supervisory authorities.

6.7 Future Perspectives on the Plasma Industry

For the Swedish plasma industry to survive, the manufacture of plasma pharmaceuticals by fractionation must achieve profitability. According to representatives of the pharmaceutical industry, the price difference between American and Swedish source plasma is of decisive importance for the future. The profitability of the plasma industry can increase if higher collection volumes are allowed and this results in lower purchasing prices for source plasma. Results from the planned Pan-European collection study will most likely have an impact in this respect.

The profitability of industrial activity also depends on how many end products are produced from the source plasma. Although a few years ago it was thought that the growing demand for plasma products was over, production has recently increased. The

introduction of recombinant factor VIII has lowered the demand for plasma derived factor concentrate. Concurrently, however, the demand for immunoglobulins has increased.

The results from the planned state-of-the-art conference, and other initiatives to review and strengthen the scientific foundation for the use of plasma products, may influence future demand. Entirely new plasma products and treatment opportunities may appear in the future. Future development may also depend on the use of other blood components, e.g. red blood cells, as a source in pharmaceutical production. Despite the introduction of recombinant products, the current opinion is that some plasma derived products cannot be replaced by genetically engineered alternatives.

6.8 International Collaboration in Blood-related Issues

There are many international organizations dealing with issues of blood and plasma donation, and the use of blood and blood products. The General Assembly of WHO, the Council of the European Union, the European Commission, the EU Pharmaceutical Authority, the EMEA, and the European Pharmacopoeia can make decisions on binding regulations and non-binding recommendations. Furthermore, e.g. the International Red Cross, the Council of Europe, and the International Society of Blood Transfusion (ISBT) have made recommendations. There are, however, few regular official contacts among the various authorities that could potentially guarantee unanimity. Rather, one can observe a certain degree of competition among the collaborating European institutions.

The regulations and numerous recommendations on blood and plasma activities lead to a particular observation. Instead of building on a systematic review of existing scientific studies, most documents are based on a consensus of high-level experts who have not referred to the underlying body of scientific literature. Often,

one expert group refers to the other, the statements of which are either accepted without further review or modified to some extent.

In future collaboration, representatives of Sweden should contribute toward establishing a process for reviewing the recommendations and regulations based on the principles of evidence-based medicine. Consensus documents issued by experts – regardless of how ”high” their reputations may be – are not sufficient. The documents should be accompanied by a systematic body of facts, available for external review. This process will increase transparency in decision making and promote effective up-dating of the respective documents.

It is also essential that the various European collaborating bodies focus their efforts on issues which are, in fact, within the mandate of their respective organizations. The work of the Council of Europe should focus mainly on ethical and humanitarian problems associated with blood services. In EU, the need to harmonize regulations – aimed to guarantee blood safety and hence enable free mobility for both blood products and for citizens of the union – is an important departure point. A more distinct distribution of roles among the organizations would both increase the quality of work by the involved committees and contribute toward issuing recommendations that better complement each other.

In Sweden, the involved authorities should be able to better coordinate the participation of experts in international groups, and establish clear guidelines for reporting. This information should then be made available to a wider audience. Since the member states must have the opportunity to create and maintain consistent policies in blood-related issues, the routines for recruiting national experts, e.g. for various EU committees, should be reviewed.

The standards that apply to scientific work should also apply to the regulatory work of the national authorities. The most favorable opportunities for exercising influence within EU will be found among the countries having effective mechanisms by which to rapidly develop a scientific basis for their opinions and decisions. The Working Group therefore suggests that the government jointly appoint the National Swedish Board of Health and Welfare, and the

Medical Products Agency, to study the scientific foundation underlying the regulations that govern blood and plasma services.

Highest priority should be given to reviewing the regulations affected by the new EU recommendations on selecting donors and testing donated blood. Concurrently, organizational structures and working procedures should be developed for scientific monitoring and decision making in related areas that are soon likely to become involved in EU collaboration, e.g. inspection and quality assurance of blood and plasma services.

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Appendices

Appendix 1. Swedish National Working Group on Blood Self-sufficiency. – EUROPEAN SELF-SUFFICIENCY IN BLOOD AND BLOOD PRODUCTS. *Balancing Supply and Demand.* Background Paper to the Statement by the Swedish Minister of Health and Social Affairs Margot Wallström at the Health Council Meeting, June 5, 1997. 28.5.1997

Appendix 2. Swedish National Working Group on Blood Self-sufficiency. - *Towards European Self-sufficiency in Plasma and Plasma Products.* Background Paper presented at the Meeting of National Experts on Blood Self-sufficiency, European Commission, DGV, Luxembourg, November 6-7, 1997. 30.10.1997.

Appendix 3. The Council's Recommendation On the Suitability of Blood- and Plasma Donors and Screening of Donated Blood Within the European Union, June 29, 1998.

Glossary

Source plasma
Plasma collected by means of a special, (usually) mechanical method, see plasmapheresis

Blood plasma
Yellow fluid, containing protein and salt, which constitutes approximately half of the blood volume

Blood product
Product manufactured on an industrial scale and derived from blood components as raw material

BSE
Bovine Spongiform Encephalopathy, brain disease in cattle, mad cow disease

CJD
Creutzfeldt-Jacob disease, brain disease in humans. nvCJD refers to the new variation of the disease, which is suspected to be transmitted from cattle with the mad cow disease

CMV
Cytomegalovirus

CPMP
Committee for Proprietary Medicinal Products, the EMEA scientific committee

EMEA
European Agency for the Evaluation of Medicinal Products, the central pharmaceutical authority of the EU

Erythrocytes
Red blood cells

EU
The European Union, association of 15 member states which have assigned extensive tasks and responsibilities to common institutions, and have developed common policies in numerous fields, e.g. public health issues

Council of Ministers (Council of the European Union, the Council)
Decision-making institution within EU. The Council of Ministers consists of one representative for each member state's government, and its constitution varies depending on the issues being discussed, e.g. the Health Council

European Pharmacopeia
Collection of quality standards developed within the European Council

European Parliament
Assembly of more than 600 directly elected representatives for the citizens of Europe

Council of Europe
Collaborative organization for 41 European countries. A central basis for the work of the Council of Europe is the human rights convention.

European Council
The leading authority in EU, consisting of the member states' governments and/or heads of state and foreign ministers, and the European Commission’s chairman and another of its members

Commission of the European Communities (European Commission)
Investigative, proposition-making, executive, and supervisory institution within EU

Evidence-based medicine
Approach within medicine emphasizing the importance of systematically compiled scientific knowledge as the foundation for medical activities

GMP
Good Manufacturing Practice

HAV
Hepatitis A Virus

HBV
Hepatitis B Virus

HCV
Hepatitis C Virus

Hemophilia
Bleeder's disease

HIV
Human Immunodeficiency Virus

HTLV
Human T Lymphotropic Virus

Recovered plasma
Plasma obtained from whole blood by separation of cells

Leucocytes
White blood cells

NAT
Nucleic acid amplification techniques, methods for multiplying nucleic acids

PCR
Polymerase chain reaction, a specific method for multiplying nucleic acids

Plasmapheresis
Method for collecting blood plasma by concurrent separation and re-transfusion of blood cells

Plasma fractionation
Industrial process for manufacturing plasma products

Plasma product
Product manufactured on an industrial scale and derived from plasma as raw material

State of the Art
Current state of knowledge, research stage

Thrombocytes
Platelets