



NATIONAL HEMOPHILIA FOUNDATION
for all bleeding and clotting disorders

MASAC Document #205
(Replaces Document #202)

**MASAC RECOMMENDATIONS CONCERNING PRODUCTS LICENSED FOR THE
TREATMENT OF HEMOPHILIA AND OTHER BLEEDING DISORDERS
(Revised November 2011)**

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Advisory Council (MASAC) on November 12, 2011, and adopted by the NHF
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I. Recommendations for Physicians Treating Patients with Hemophilia A and B, von Willebrand Disease, and other Congenital Bleeding Disorders:

A. Treatment of Hemophilia A

1. Recombinant Factor VIII Concentrates

Recombinant (r) FVIII is produced by well-established hamster cell lines that have been transfected with the gene for human FVIII.(1,2) Two recombinant factor VIII products have the B domain deleted from the factor VIII gene before it is inserted into Chinese hamster ovary cells (3). First generation rFVIII contains animal and/or human plasma-derived proteins in the cell culture medium and in the final formulation vial. Second generation rFVIII contains animal or human plasma proteins in the medium but not in the final formulation, while third generation rFVIII does not contain any animal or human plasma-derived proteins in the culture medium or in the final formulation vial.

The risk of human viral contamination associated with recombinant FVIII is definitely much lower than for plasma-derived FVIII products. No seroconversions to HIV, HBV, or HCV have been reported with any of the currently available products; thus recombinant factor VIII products are the recommended treatment of choice for patients with hemophilia A. (Table I.A.)

2. Plasma-Derived Factor VIII Concentrates

Improved viral-depleting processes and donor screening practices have resulted in plasma-derived (pd) FVIII products that have greatly reduced risk for transmission of human immunodeficiency virus and hepatitis B and C. No seroconversions to HIV, HBV, or HCV have been reported with any of the pdFVIII products currently marketed in the United States, including products that are heated in aqueous solution (pasteurized), solvent-detergent treated, and/or immunoaffinity purified. Thus, each of these methods appears to have greatly reduced the risk of viral transmission compared with older methods of viral inactivation (4-6). There remains the *possibility* of HIV-1, HIV-2, or hepatitis B or C virus transmission with the use of currently marketed, viral-inactivated, plasma-derived products. The non-lipid enveloped viruses human parvovirus B19 and hepatitis A virus were also transmitted by pdFVIII (7-9); additional steps such as viral filtration have been added to reduce these risks as well. (Table I.B.)

3. Cryoprecipitate Not Recommended

FVIII products are available that are manufactured by recombinant technology and thus theoretically do not transmit human viruses. Moreover, methods of viral inactivation (pasteurization, solvent-detergent treatment, immunoaffinity purification) have resulted in a reduced risk of HIV and hepatitis B and C transmission with plasma-derived factor VIII concentrates (5-6, 10-12).

For these reasons, cryoprecipitate should not be used as a treatment alternative. Despite donor screening by nucleic acid testing (NAT) for HIV-1, HBV, and HCV, cryoprecipitate might still be infectious. While the current estimate for the risk of HIV infection from a single unit of blood is one in 1,000,000 donations, the risk of HCV transmission is somewhat higher,

approximately 1 in 900,000 (13).

4. Treatment of Mild Hemophilia A

Desmopressin (DDAVP) should be used whenever possible for patients with mild hemophilia A. DDAVP is available in both a parenteral form (DDAVP Injection) and a highly concentrated intranasal spray formulation (Stimate Nasal Spray). (14) (Table III.A.)

Desmopressin should not be used in certain categories of patients. Children under the age of 2, pregnant women, and patients with mild hemophilia A in whom desmopressin does not provide adequate Factor VIII levels should be treated as per section I.A.1 or I.A.2 above.

B. Treatment of Hemophilia B

1. Recombinant Factor IX Concentrate

Recombinant factor IX (rFIX) is produced in Chinese hamster ovary cells; no human or animal plasma-derived proteins are used in the manufacturing process, and it is stabilized with sucrose (third generation product). Thus the risk of human blood-borne viral contamination is much lower than for plasma-derived factor IX concentrates. (15) Recombinant factor IX is considered to be the treatment of choice for patients with hemophilia B. (Table II.A.)

2. Plasma-Derived Factor IX Concentrates

Improved viral depleting processes and donor screening practices have resulted in plasma-derived (pd) FIX products with greatly reduced risk for HIV, HBV, and HCV transmission (16). Viral attenuation methods used in the production of pdFIX products that appear to be effective for reducing the risk of HIV and hepatitis are dry heating at 60°C for 144 hours, solvent-detergent treatment, vapor treatment, and sodium thiocyanate plus ultrafiltration. Purification steps involved in the preparation of the more purified pd-coagulation FIX products are associated with loss of several additional logs of virus. There remains the slight possibility of viral transmission with the currently marketed viral-inactivated, plasma-derived products. Transmission of human parvovirus B19 and hepatitis A virus by these products did occur, but the risk has been reduced with additional viral attenuation methods such as ultrafiltration. (Table II.B.)

C. Treatment of von Willebrand Disease (VWD)

1. Desmopressin

Most persons with von Willebrand disease type 1 may be treated with desmopressin, given either parenterally (DDAVP Injection) or by highly concentrated nasal spray (Stimate Nasal Spray). Some Type 2A patients may respond to DDAVP; a clinical test should be done to determine whether DDAVP can be used for these patients. (14) (Table III.A.)

2. VWF-Containing Factor VIII Concentrates

Use of a viral-inactivated pdFVIII preparation rich in von Willebrand factor is recommended in certain types of vWD that do not respond to DDAVP i.e. Type 2B VWD and Type 3 VWD. Its

use is also recommended for use in Type 1 or 2A VWD patients who have become transiently unresponsive to DDAVP and in surgical situations, especially in young patients (17-21). Alphanate, Humate-P, and Wilate have been licensed by the FDA for use in von Willebrand disease; in certain patients, Koate-DVI may also be effective. (Table III.B.)

3. Cryoprecipitate Not Recommended

Because it has not undergone any viral attenuation steps, cryoprecipitate should not be used to treat patients with vWD except in life- and limb-threatening emergencies when VWD-containing factor VIII concentrate is not immediately available.

D. Treatment of Patients with Inhibitors to Factor VIII or IX

Inhibitor development is the most common and most severe complication of hemophilia treatment. The following products have been licensed for treatment of bleeding episodes in patients with inhibitors. However, these products are not interchangeable. Choice of product depends on multiple factors, including type of inhibitor (low- or high-responding), current titer of inhibitor, location of the bleed, and previous response to these products. For high-titer inhibitors, immune tolerance induction is the best option for inhibitor eradication. Consultation with a Hemophilia Treatment Center is strongly recommended. (22)

1. Activated Prothrombin Complex Concentrate (aPCC)

aPCC contains activated factors IIa, VIIa, and Xa. These factors are able to bypass an inhibitor to factor VIII or factor IX in order to promote hemostasis. This product is derived from human plasma and is treated with vapor steam heat to eliminate viruses (23). (Table IV.A.)

2. Recombinant Factor VIIa Concentrate

Recombinant factor VIIa is licensed for use in patients with inhibitors to factor VIII or IX. It is produced by baby hamster kidney cells; animal but not human proteins are used in its production. It is stabilized with mannitol (second generation recombinant product). Thus the risk of transmission of human viruses is essentially zero (24). (Table IV.B.)

3. Reduction of Thromboembolic Risk

Thrombotic risks exist with the use of both of these products. It is important that physicians and patients not exceed recommended doses to reduce the risk of thromboses.

E. Treatment of Patients with Rare Congenital Bleeding Disorders

1. Fibrinogen (Factor I) Deficiency

a. Plasma-derived Fibrinogen Concentrate

Plasma-derived fibrinogen concentrate is heated in aqueous solution (pasteurized) at 60°C for 20 hours. It can be used to treat patients with congenital hypofibrinogenemia and afibrinogenemia but not dysfibrinogenemia. (25) (Table V.A.)

2. Factor VII Deficiency

a. Recombinant Factor VIIa Concentrate

Recombinant factor VIIa is produced by baby hamster kidney cells. Animal but not human protein is used in its production; it is stabilized with mannitol (second generation recombinant product). Thus the risk of transmission of human viruses is essentially zero. (24) It can be used to treat patients with congenital factor VII deficiency. (Table V.B.)

3. Factor XIII Deficiency

a. Plasma-derived Factor XIII concentrate

Plasma-derived Factor XIII concentrate is heated in aqueous solution (pasteurized) at 60°C for 10 hours and undergoes ion exchange chromatography. It can be used for patients with absent or decreased levels of FXIII. (26) (Table V.C)

4. Other Rare Clotting Factor Deficiencies:

Although there is no product currently licensed to treat other rare bleeding disorders, the following products are listed to enable healthcare providers to advise and treat these patients.

a. Prothrombin Complex Concentrates

Plasma-derived prothrombin complex concentrates (pd-PCCs) can be used to treat patients with deficiencies of factors II and X. It should be noted, however, that these products vary considerably in the amounts of these factors that they contain. Not only is there a marked difference in factor content between the different commercial preparations, but factor content varies between lots produced by the same manufacturer.(27) (Table V.D.)

b. Factor X concentrate is a plasma-derived concentrate being tested in the US for treatment of Factor X deficiency.

5. Rare Clotting Disorders

a. Antithrombin deficiency

There are now two products available for treatment of Antithrombin deficiency. One is a recombinant product produced by introducing the human Antithrombin gene into the mammary glands of goats. Antithrombin is secreted into the goat milk and then extracted, purified, and lyophilized. It is subjected to three viral attenuation steps. The second product is a plasma-derived human Antithrombin that is pasteurized as a viral attenuation method. (Table VI.A.)

b. Protein C deficiency

There is now a plasma-derived Protein C product licensed in the U.S. to treat Protein C deficiency. It has three viral attenuation steps. (Table VI.B.)

6. The following single-donor blood components may be used for treating rare bleeding disorders.

a. Fresh frozen plasma (FFP) can be used to treat patients with deficiencies of any of the clotting factors for which specific clotting factor concentrates are not available. One type of FFP, donor retested FFP, is produced from single units of plasma; the donor must return and test negative on a second donation in order for the first donation to be released. This product is available from some community blood centers. (Table VII.A.)

- b. Cryoprecipitate is the only currently available product for dysfibrinogenemia. Because it has not undergone any viral attenuation steps, cryoprecipitate should not be used to treat patients with factor XIII deficiency except in life- and limb-threatening emergencies when Factor XIII concentrate is not immediately available. (See Section E.3.a. above) (Table VII.B.)

F. Vaccination for Hepatitis A and B

1. Hepatitis B vaccine is recommended for all children by the American Academy of Pediatrics (AAP). In persons with hemophilia and other congenital bleeding disorders, this immunization is particularly important and should be started at birth or at the time of diagnosis if the individual has not been previously immunized. Primary immune response should be documented.
2. Hepatitis A vaccine is recommended for all children over the age of 1 year by the AAP. Older individuals with hemophilia and other congenital bleeding disorders who are HAV seronegative should also be immunized. (28-29)

G. Ancillary Medications

1. Vitamin K. Newborn infants with hemophilia and other bleeding disorders should be given a dose of Vitamin K in the delivery room per the recommendations of the American Academy of Pediatrics. For infants with hemophilia, this may be given subcutaneously.
2. Antifibrinolytics
 - a. Amino caproic acid (Amicar) is an oral antifibrinolytic agent that can be used to treat mouth bleeds. It comes as a syrup with a concentration of 1.25 g/5ml. The dose is 50-100 mg/kg. Note that a dose of factor concentrate must be given first to form the clot; amino caproic acid is then given every 6 hours to preserve the clot until healing has taken place (10-14 days).
 - b. Transexemic acid (Lysteda) is an oral antifibrinolytic agent that is used to treat menorrhagia. The dose is 1300 mg (two 650 mg tablets) every 8 hours for 5 days during menstruation. Note that women taking Lysteda should not take plasma-derived Factor IX Complex Concentrates or plasma-derived activated Prothrombin Complex Concentrates for inhibitors.
3. Individuals with inherited bleeding disorders should not use aspirin, ibuprofen, or any medication containing either of these two drugs, or anti-platelet agents unless recommended by any one of their physicians in consultation with their treating hematologist.

H. Other Issues of Importance

1. When choosing the appropriate products for their patients with hemophilia, physicians will need to continue to exercise their best judgment based on their assessment of emerging data.
2. If a previously seronegative patient has a confirmed seroconversion to any blood-borne infectious agent that is felt by the local public health department to possibly be due to use of a blood component or blood product, this should be immediately reported to the FDA, to the manufacturer of the product received, and to the CDC.
2. Patients should enroll in the Universal Data Collection (UDC) study of the CDC to ensure continued maintenance of the UDC serum bank, which will enable quick evaluation of possible transmission of a new pathogen by plasma-derived or recombinant products.
3. Patients should enroll in the voluntary National Notification System in order to be notified

- promptly of any recalls of factor products they may be using.
4. Decisions about the selection of products for treatment of hemophilia are complicated for patients, families, and treating physicians. Thus, patient education, psychosocial support, and financial counseling are critical components of comprehensive care.

II. Recommendations to Manufacturers of Coagulation Products

- A. We recommend continued vigilance in donor screening and donor testing at blood and plasma collection facilities.
 1. Plasma must not be collected in donor centers that draw from population groups in which there is a relatively high incidence of hepatitis and AIDS.
 2. Manufacturers should disclose the incidence of hepatitis and HIV infection at individual plasma collection centers. Maximum allowable viral marker rates for the donor population for anti-HCV, anti-HIV, and HBsAg should be established.
 3. Manufacturers should use only plasma that is collected by facilities qualified to receive the International Quality Plasma Program (IQPP) certification of the Plasma Protein Therapeutics Association (PPTA) and processed by fractionators certified by the QSEAL program of the PPTA in accordance with recommendations to hemophilia treatment centers (see “MASAC Recommendations on the IQPP and QSEAL Programs of the Plasma Protein Therapeutics Association,” MASAC Document #139).
 4. Plasma should not be accepted for further processing until the donor has successfully passed at least two health history interviews and screening tests within a specified time period.
 5. All donations should be held for at least 60 days. If during this period the donor seroconverts and tests positive for a virus or is otherwise disqualified, the held donation should be destroyed.
 6. Donors diagnosed with CJD or vCJD or who are at risk for CJD or vCJD should continue to be deferred from donating blood and plasma. If such individuals are identified after donation, all products containing their plasma, including albumin used as an excipient (stabilizer) in plasma-derived and recombinant products, should continue to be quarantined. If the product has been released into the distribution chain, it should be withdrawn and end-users notified through the National Notification System.
- B. Increased efforts should be made to exclude from further processing the plasma from donors who are infected with HIV, HBV, HCV, HAV, human parvovirus, and vCJD.
 1. Tests to identify viral nucleic acids (polymerase chain reaction [PCR] and other genome amplification tests) should be implemented expediently for all plasma that will be processed into clotting factor concentrates.
 2. Priority of test implementation should focus on viral agents that are not inactivated by current viral elimination techniques, namely, HAV and parvovirus B19.
 3. Nucleic acid testing (NAT) offers significant incremental sensitivity over the HIV antigen test and serologic tests for HIV, HCV, and HBV. This can best be accomplished by testing individual donors or very small donor mini-pools.
 4. Infected donors should be notified of their status in an appropriate manner.
 5. Efforts to develop a test to identify donors potentially infectious for vCJD should be given high priority.

- C. Plasma pool size should be decreased to levels approaching 15,000 donors per lot of finished product.
 - 1. Reduction in the number of donors in final lots of product will decrease the spread of a new infectious threat that is transmitted via plasma products.
 - 2. Manufacturers should disclose the number of donors in each lot of their products.
 - 3. Albumin used as an excipient in purified coagulation products should be obtained from the same plasma pool to eliminate exposure to additional donors.
 - 4. Reduction in the number of donors in lots of product will decrease the amount of product withdrawn or quarantined as a result of a donor with a potentially transmittable disease.

- D. Improved viral inactivation and elimination procedures are required in coagulation products.
 - 1. All efforts should be made to remove human albumin from recombinant factor VIII products.
 - 2. Increased efforts should be made to eliminate human and bovine proteins from the manufacturing process of recombinant products.
 - 3. Research to identify methods to eliminate the infectivity of pathogenic non-enveloped viruses and vCJD prions that may appear in the blood supply should continue to be given high priority.
 - 4. New methods must be identified to minimize the chance of transmitting new agents which may emerge in the blood supply.

- E. Methods of screening for new and emerging threats to the blood supply should be developed.
 - 1. Nucleic acid tests for emerging threats such as West Nile Virus and Chagas Disease should be developed as expeditiously as possible.
 - 2. Manufacturers should conduct specific tests with these agents to demonstrate that they are inactivated by their specific manufacturing methods.

- F. Reporting of adverse events associated with coagulation products should occur more expeditiously.
 - 1. Manufacturers should report suspected viral transmission events to the FDA monthly.
 - 2. Manufacturers should cooperate fully with the FDA and CDC in their investigations to determine if their product is responsible for a viral infection.
 - 3. New products are often approved after small numbers of patients are evaluated in clinical trials. Manufacturers are strongly encouraged to conduct Phase IV post-licensure studies for efficacy and for surveillance for viral infections.
 - 4. The FDA has brought standards for the manufacture of coagulation products up to the level of other drugs regulated by the FDA. Manufacturers should anticipate that the FDA is seeking evidence of ongoing enhanced training programs, manufacturing controls, quality assurance, and quality control.

- G. Notification to consumers and their health care providers of safety and regulatory problems must occur in a more expeditious fashion.
 - 1. Manufacturers are responsible for notifying their consignees of any withdrawals. The FDA has defined the consignee as "anyone who received, purchased, or used the product being recalled" (21 CFR 7.3(n)) e.g., the customer, direct account, or person with a coagulation disorder and his or her healthcare provider. Manufacturers should accept the responsibility

- for notifying their customers if they have purchased a product that is out of compliance.
2. Notification to customers must occur early in the investigation. While we recognize that occasionally a product may be exonerated from disease transmission, it is vital to err on the side of safety and remove a product under investigation from its point of use, including patients' homes.
 3. While the voluntary National Notification System implemented by some companies does provide a good mechanism for notification, it should not be considered a substitute for the responsibility²the manufacturers have to notify their customers directly.
 4. Intermediaries, including home care companies and 340B programs, must keep accurate records of the lots their customers use and have systems in place to notify patients and their healthcare providers immediately upon learning of a compromised product lot.
- H. Research and development of improved coagulation products that would expedite the transition to total prophylaxis for all persons with coagulation disorders are strongly encouraged.
1. Licensed recombinant products to treat patients with von Willebrand disease and patients with rare bleeding disorders are urgently needed.
 2. Recombinant products should be developed that could be taken less frequently or administered by routes other than intravenously.
 3. Methods to manufacture coagulation products more inexpensively, such as use of transgenic animals, would increase supply and availability worldwide.
 4. Costs of coagulation products should be reduced.
 5. NHF has endorsed the development of clinical trials in gene therapy to cure bleeding disorders. Manufacturers should facilitate the clinical development of this technology.
- I. Manufacturers should take necessary steps to ensure the continued availability of plasma-derived clotting factor concentrates for individuals with rare bleeding disorders.
1. Such concentrates are safer than the alternatives of fresh-frozen plasma (FFP) and cryoprecipitate, which are not virally attenuated.
 2. Such concentrates provide the ability to raise clotting factor levels to 100% without the risk of volume overload, which is another drawback of FFP.
 3. Such concentrates allow for prophylactic treatment, if indicated by severity of the disease and frequency of bleeding episodes.
 4. Such concentrates provide the convenience of storage and treatment at home and while traveling.
- J. Manufacturers should work towards development of pathogen-safe specific clotting factor concentrates for each of the rare bleeding disorders. These replacement products can be either plasma-derived or recombinant.
1. Such clotting factor concentrates would allow for individualized treatment of each specific clotting factor deficiency.
 2. Such clotting factor concentrates would allow for increased safety from possible transmission of viral and other infectious agents.

III. Recommendations to the Food and Drug Administration

The Food and Drug Administration is responsible for regulating the manufacturers of coagulation products to ensure that licensed products are safe and effective. Many of our recommendations for

manufacturers should be regulated proactively by the FDA.

A. Plasma Collection

1. The FDA should establish stricter guidelines for the collection of plasma, to include the use of plasma from repeat donors only, inventory hold, establishment and publication of viral marker rate standards for plasma collection centers, and establishment of sensitive genome amplification tests for infectious agents such as West Nile Virus and Chagas Disease.
2. The FDA should implement pool size restrictions along the lines of their proposal in 1996 of 15,000 donors for source plasma.

B. Elimination of Infectious Agents

1. Research to identify improved inactivation and elimination techniques for non-lipid enveloped viruses should be actively encouraged by the FDA.
2. Validation studies to identify the amount of removal of vCJD prions should be recommended the FDA to each manufacturer for each of their products.
3. The FDA should work with the National Heart, Lung, and Blood Institute and industry to ensure that sufficient resources are available to develop inactivation techniques for vCJD prions.

C. Investigation and Reporting of Suspected Transmissions

1. The FDA should maintain sufficient compliance checks to ensure that manufacturers are expeditiously reporting any and all suspected infections associated with coagulation products.
2. The FDA should work with the CDC to investigate any suspected viral transmission via coagulation products. Patients and providers should be included as advisors in the early stages of each investigation to provide relevant perspectives.
3. Products under investigation should be assumed to be implicated in pathogen transmission until proven otherwise. Accordingly, these products should be removed from the distribution path, including removing them from patients' homes.
4. The FDA should communicate promptly with consumer organizations such as NHF whenever an event occurs, such as a recall, voluntary withdrawal, consent decree or plant closure, which could have an impact on the supply and availability of clotting factor concen

D. Bar Coding and Notification

1. The FDA should require the use of barcoding to identify coagulation products with regards to lot number, number of units, and expiration date in order to facilitate accurate tracking and dispensing of product and accurate, timely recording of usage in the hospital and at home.
2. The FDA should enforce the implementation and maintenance of a notification system that follows the product through its entire distribution pathway to the end use

E. Expedited Review and Harmonization

1. All products offering incremental safety and efficacy advantages to the bleeding disorders community should have expedited regulatory review.
2. The FDA should work with the EMEA to harmonize requirements for licensing approval of clotting factor concentrates for use in individuals with rare bleeding disorders.

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GLOSSARY TO MASAC RECOMMENDATIONS

Activated Prothrombin Complex Concentrate (aPCC)

One plasma-derived prothrombin complex concentrate is purposely "activated" so that it contains some FIX, FX, and FII in active form (FIXa, FXa, and FIIa). FEIBA NF is to be used in inhibitor patients only.

Coagulation Factor IX Concentrates

Plasma-derived Factor IX concentrates that contain very little or no coagulation factors other than FIX include AlphaNine SD and Mononine.

Desmopressin (DDAVP, Stimate)

Desmopressin acetate is a synthetic analogue of the natural pituitary antidiuretic hormone, 8-arginine vasopressin. When given to persons who have the capability of producing some FVIII or vWF, the drug effects a rapid, transient increase in FVIII and vWF. It can be given intravenously, subcutaneously, or by intranasal spray. The intranasal spray form is called Stimate Nasal Spray.

Dry Heat-treated Concentrates

No currently available FVIII or FIX concentrates are exclusively dry heat-treated. However, dry heat treating may be used in conjunction with other viral attenuation modalities.

Factor VIII Concentrates Rich in von Willebrand Factor

In certain of the plasma-derived intermediate purity FVIII concentrates, the hemostatically important high molecular weight multimers of von Willebrand factor are preserved. Three products, Alphanate, Humate-P, and Wilate have been approved by the FDA for use in patients with von Willebrand disease. One other product, Koate-DVI, while not FDA-approved for vWD, may also be effective in preventing or controlling bleeding in some persons with VWD.

First Generation Recombinant Factor Concentrates

Animal and/or human plasma-derived proteins are used in the cell culture medium and in the final formulation of these concentrates. An example is Recombinate.

Immunoaffinity Purified Concentrates

Plasma-derived Factor VIII and FIX concentrates that are purified using murine monoclonal antibodies attached to an affinity matrix. Viral attenuation is augmented by pasteurization (Monoclote P), by solvent/detergent treatment (Hemofil M), or by sodium thiocyanate and ultrafiltration (Mononine). **Intermediate Purity Factor Concentrates**

Plasma-derived factor concentrates that contain several clotting factors and plasma proteins in addition to the assayed factor. Examples include Alphanate, Bebulin, Bebulin VH, Humate P, Koate DVI, and Profilnine SD.

Pasteurization (Heated in Aqueous Solution)

Plasma-derived factor concentrates that are heated for 10-20 hours at 60°C in aqueous solution in the presence of stabilizers such as albumin, sucrose, or neutral amino acids include Corifact, Humate-P, Monoclote P, and RiaSTAP.

Plasma-derived Factor Concentrates (pdF)

Factor concentrates that are extracted from human plasma. They are treated by several methods to attenuate or eliminate potentially infectious agents such as viruses.

Prothrombin Complex Concentrates (PCC)

Intermediate purity, plasma-derived prothrombin complex concentrates (PCC) contain factors II, VII, IX, and X and proteins C and S plus small amounts of activated coagulation factors. Examples of these products include Bebulin, Bebulin VH, and Profilnine SD.

Recombinant Factor Concentrates (rF)

Recombinant factor concentrate refers to genetically engineered concentrate that is not derived from human or animal plasma. In the case of recombinant FVIII, the gene encoding normal human FVIII is inserted into hamster cell nuclei (cells obtained from well-established baby hamster kidney cell lines or Chinese hamster ovary cells). The hamster cells then produce FVIII that is indistinguishable from plasma-derived human FVIII. Currently licensed rFVIII products are Advate, Helixate FS, Kogenate FS, and Recombinate. One other rFVIII product, Xyntha, lacks the B domain of FVIII. A recombinant FIX product, BeneFIX, is produced by Chinese hamster ovary cells. A recombinant FVIIa product, NovoSevenRT, is produced by baby hamster kidney cells. It is used to treat patients with inhibitors to factors VIII and IX as well as patients with inherited Factor VII deficiency. A recombinant Antithrombin product is produced by transfecting goat mammary glands with the human Antithrombin gene and then separating out the human Antithrombin secreted in the goats' milk. The Atryn is lyophilized into a powder that is reconstituted with sterile water for injection.

Second Generation Recombinant Factor Concentrates

Animal and/or human plasma-derived proteins are used in the cell culture medium but not in the final formulation of these concentrates. The product is stabilized with a sugar such as mannitol or sucrose. Examples include Helixate FS, Kogenate FS, and NovoSevenRT.

Solvent Detergent Treated Concentrates

Plasma-derived factor concentrates that are manufactured using combinations of the solvent, Tri(n-Butyl) Phosphate (TNBP), with a detergent, such as polysorbate 80 or Triton-X-100, to inactivate lipid-enveloped viral contaminants (lipid-enveloped viruses include HIV, HBV, HCV). The pdFVIII concentrates Alphanate and Koate-DVI are solvent-detergent treated using TNBP and Polysorbate 80. Hemofil M is solvent-detergent treated with TNBP and Triton X-100. A coagulation FIX concentrate (AlphaNine SD) is solvent-detergent treated using TNBP and Polysorbate 80, as is the prothrombin complex concentrate Profilnine SD.

Third Generation Recombinant Factor Concentrates

No animal or human plasma-derived protein is used in the cell culture medium or in the final formulation of these products. The product is stabilized with a sugar such as sucrose or trehalose. Examples include Advate, BeneFIX, and Xyntha.

Vapor-treated Concentrates

Two plasma-derived coagulation products currently licensed in the U.S. use vapor (steam) treatment for viral attenuation. Bebulin and BebulinVH, prothrombin complex concentrates, and FEIBA NF, an activated prothrombin complex concentrate, are both vapor treated for 10 hours at 60°C and 190 mbar pressure, followed by 1 hour at 80°C under 375 mbar pressure.