



**NATIONAL HEMOPHILIA FOUNDATION**  
*for all bleeding disorders*

MASAC Document #237  
(Replaces Document #235)

**MASAC RECOMMENDATIONS CONCERNING PRODUCTS LICENSED FOR THE  
TREATMENT OF HEMOPHILIA AND OTHER BLEEDING DISORDERS  
(Revised August 2015)**

*The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on August 15, 2015, and adopted by the NHF Board of Directors on November 13, 2015.*

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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. Native Recombinant Factor VIII Concentrates**

Recombinant (r) FVIII is produced by two well-established hamster cell lines, baby hamster kidney (BHK) and Chinese hamster ovary (CHO), that have been transfected with the gene for human FVIII. (1,2) One recombinant factor VIII product has the B domain deleted from the factor VIII gene before it is inserted into CHO cells; in another, the B domain is truncated (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 culture 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. Recombinant factor VIII products are the recommended treatment of choice for patients with hemophilia A. (Table I.A.)

### **2. Prolonged half-life Recombinant Factor VIII Concentrate**

Prolonged half-life recombinant Factor VIII is produced in a human embryonic kidney (HEK) cell line. It is fused with the Fc fragment of human IgG, which inhibits lysosomal degradation by endothelial cells, thus prolonging its half-life in the circulation. There are no human or animal proteins employed in its production. It is stabilized with sucrose. Recombinant factor VIII products are the recommended treatment of choice for patients with hemophilia A. (32) (Table I.B.)

### **3. 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.C., Table I.D.)

4. 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. The current estimate for the risk of HIV or HCV infection from a single unit of blood is approximately one in 1,000,000 donations (13).

5. Treatment of Mild Hemophilia A

Desmopressin (DDAVP) may be used for patients with mild hemophilia A who have been documented by a DDAVP trial to have a rise in FVIII. DDAVP is available in both a parenteral form (DDAVP Injection) and a highly concentrated intranasal spray formulation (Stimate Nasal Spray). (14) (Table I.E.)

Desmopressin should not be used in certain categories of patients. Children under the age of 2 years 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 CHO 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 products are the recommended treatment of choice for patients with hemophilia B. (Table II.A.)

2. Prolonged half-life Recombinant Factor IX Concentrate

Prolonged half-life recombinant Factor IX is produced in an HEK cell line. It is fused with the Fc fragment of human IgG, which inhibits lysosomal degradation by endothelial cells, thus prolonging its half-life in the circulation. There are no human or animal proteins employed in its production. It is stabilized with sucrose and mannitol. Recombinant factor IX products are the recommended treatment of choice for patients with hemophilia B. (31) (Table II.B.)

3. 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 nanofiltration. (Table II.C.)

### 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 DDAVP trial 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 children under the age of 2 years. (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 Inherited Hemophilia A or B and Inhibitors to Factor VIII or Factor IX

Inhibitor development is the most common and most severe complication of treatment for patients with inherited hemophilia A or B. The following products have been licensed for treatment of bleeding episodes in these 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. FEIBA (Activated Prothrombin Complex Concentrate [aPCC])

FEIBA 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 and nanofiltration to eliminate viruses (23). (Table IV.A.)

#### 2. NovoSeven RT (Recombinant Activated Factor VIIa Concentrate)

Recombinant activated factor VIIa is licensed for use in patients with inherited hemophilia A or B and inhibitors to factor VIII or IX. It is produced by baby hamster kidney cells; newborn calf serum is used in the culture medium; no human or other animal proteins are used in its final formulation vial. 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. Thromboembolic Risk

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

E. Treatment of Patients with Acquired Hemophilia A

Under certain conditions, individuals who were not born with hemophilia may develop antibodies or inhibitors that cause destruction of factor VIII, resulting in clinical bleeding due to very low levels of this clotting factor. Such inhibitors may be seen in patients with cancer, lupus erythematosus, and other autoimmune disorders. These individuals should be treated by hematologists experienced in the management of such patients. These patients may be treated with the following recombinant clotting factor concentrates:

1. NovoSevenRT is a recombinant activated human factor VIIa (rhFVIIa) that is licensed for use in patients with both inherited hemophilia A or B and inhibitors and in patients with acquired hemophilia A due to inhibitors. It is a second-generation recombinant product. (Table V.A.)
2. Obizur is a recombinant porcine factor VIII (rpFVIII) that is produced in BHK cells transfected with the B-domain deleted porcine gene for factor VIII. This is a second-generation recombinant product that is approved by the FDA only for use in acquired hemophilia A. Often the human FVIII inhibitor does not cross-react with the porcine species of FVIII, thus allowing for measurable factor levels and cessation of bleeding with Obizur treatment. (33) (Table V.A.)

F. 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 VI.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 afibrinogenemia except in life- and limb-threatening emergencies when fibrinogen concentrate is not immediately available. (Table VIII.B.)

2. Factor VII Deficiency

a. Recombinant Activated Factor VIIa Concentrate

Recombinant activated factor VIIa is produced by baby hamster kidney cells.

Newborn calf serum is used in the culture medium; no human or other animal 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 VI.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 VI.C.)

b. Recombinant Factor XIII-A subunit concentrate

Recombinant Factor XIII-A subunit (rFXIII-A) concentrate is produced in yeast. No human or animal-derived products are used in the production vat or in the final vial. It is stabilized with sucrose in the final vial. This product is approved for use in individuals who lack FXIII-A subunit. It will not work in those patients who lack FXIII-B subunit. (27) (Table VI.D.)

c. Cryoprecipitate

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. (Table VIII.B.)

4. Other Rare Bleeding Disorders:

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.(28) (Table VI.E.)

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.

1. One is a recombinant 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. (Table VII.A.)

2. The second product is a plasma-derived human Antithrombin that is pasteurized as a viral attenuation method. (Table VII.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 VII.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.
    1. 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 VIII.A.)
    2. A second type of frozen plasma has now been licensed in the US (trade name Octaplas™). Plasma from 630-1520 donors is pooled, treated with solvent/detergent and subjected to prion affinity ligand chromatography, and then frozen in 200-ml bags. It must be given as blood group specific frozen plasma. (Table VIII.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 afibrinogenemia or factor XIII deficiency except in life- and limb-threatening emergencies when Fibrinogen concentrate or Factor XIII concentrate is not immediately available. (See Section F.1.b. and F.3.a. above) (Table VIII.B.)

#### 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. Aminocaproic 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; aminocaproic acid is then given every 6 hours to preserve the clot until healing has taken place(10-14 days).(Table IX.A.)
  - b. Tranexamic 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. (Table IX.B.)
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 one of their physicians in consultation with their treating hematologist.

## H. 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. (29-30)

## I. Other Issues of Importance

1. Decisions about the selection of products for treatment of hemophilia are complicated for patients, families, and treating physicians. 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. Education, psychosocial support, and financial counseling for patients and families are critical components of comprehensive care.
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.
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.

## 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. Manufacturers of plasma-derived products 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).
  2. Donors diagnosed with CJD or v CJD 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. Efforts should continue to exclude from further processing the plasma from donors who are

infected with HIV, HBV, HCV, HAV, human parvovirus, and vCJD.

1. Priority of test implementation should focus on viral agents that are not inactivated by current viral elimination techniques, namely, HAV and parvovirus B19.
  2. Efforts to develop a test to identify donors potentially infectious for vCJD should be given high priority.
- C. Improved viral inactivation and elimination procedures are required in coagulation products.
1. All recombinant products made with human or animal proteins, including use of albumin in the final formulation, should be phased out expeditiously.<sup>2</sup>New methods must be identified to minimize the chance of transmitting new agents which may emerge in the blood supply.
  2. Research to identify methods to eliminate the infectivity of the vCJD prions that may appear in the blood supply should continue to be given high priority.
- D. Methods of screening for new and emerging threats to the blood supply should be developed.
1. Manufacturers should conduct specific tests with these agents to demonstrate that they are inactivated by their specific manufacturing methods.
- E. 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. Although inhibitors are expected serious adverse events, they should be reported more frequently than the yearly reports to FDA
  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 of inhibitor development and other expected and unexpected serious adverse events.
- F. 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 any investigation.
  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 responsibility the 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.

- G. 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 continue to be developed that could be taken less frequently and administered by routes other than intravenously.
  3. As improvements in production efficiencies are made, cost reductions of coagulation products should be passed on to the consumer.
  4. Biosimilar FVIII and FIX products are now being introduced and should be a vehicle for substantial cost reductions, as they are in all other therapeutic areas.
  5. Inhibitor development is the single most important complication of treatment of Hemophilia A and B. Biotechnology and Pharmaceutical companies should apply their resources toward technologies which would limit the development of this complication.
  6. NHF has endorsed the development of clinical trials in gene therapy to cure bleeding disorders. Biotechnology and Pharmaceutical companies should facilitate the clinical development of these technologies.
- H. 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.
- I. 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. 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 by 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.

#### B. Investigation and Reporting of Complications of Therapies

1. The FDA should maintain sufficient compliance checks to ensure that manufacturers are expeditiously reporting any and all suspected infections, inhibitor development from clinical trials, and any other unexpected serious adverse events associated with coagulation products, both established and newer prolonged half life agents.
2. 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, concentrates.

#### C. 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. This is especially important in the design of pivotal clinical studies in adults and children, including previously untransfused patients (PUPs).

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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 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.

### **Prolonged Half-life Recombinant Factor Concentrate**

A recombinant factor molecule is fused to another protein, such as human albumin or the Fc fragment of human IgG1. The fusion is accomplished by adding the gene for the human fusion protein to the gene for factor VIII or IX before the factor gene is inserted into a cell line for production of the recombinant fusion protein factor molecule. The purpose of adding the fusion protein is to prolong the half-life of the infused factor in the circulation. Examples are Alprolix and Eloctate.

### **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 (Monoclata 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, Humate P, Koate DVI, and Profilnine.

#### **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, Monoclate 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 and Profilnine.

#### **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. Two recombinant FIX products, BeneFIX and Rixubis, are 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 FXIII-A subunit product, Tretten, is available to treat patients with FXIII-A subunit deficiency. A recombinant Antithrombin product, ATryn, is produced by transfecting goat mammary glands with the human Antithrombin gene and then separating out the human Antithrombin secreted in the goats' milk. 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.

### **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, Alprolix, BeneFIX, Rixubis, and Xyntha.

### **Vapor-treated Concentrates**

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