

**MASAC RECOMMENDATIONS CONCERNING THE TREATMENT OF
HEMOPHILIA AND OTHER BLEEDING DISORDERS
(Revised November 2003)**

The following recommendations were approved by the Medical and Scientific Advisory Council (MASAC) on, November 8, 2003, and adopted by the NHF Board of Directors on November 9, 2003.

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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) One recombinant factor VIII product has 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 the third generation does not contain any animal or human plasma-derived proteins in the culture medium or in the final 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 IA)

2. Plasma-Derived Factor VIII Concentrates

Improved viral-depleting processes and donor screening practices have resulted in plasma-derived FVIII products with 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 FVIII 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 (7-9): additional steps such as viral filtration have been added to reduce these risks as well. (Table IB)

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, 11-13).

For these reasons, cryoprecipitate should not be used as a treatment alternative. Despite donor screening by nucleic acid testing (NAT) for HIV-1, HIV-2, 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 (14).

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). (Table IV)

Children under the age of 2, pregnant women, and patients 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 its manufacturing process, and it is stabilized with sucrose (third generation product). Thus the risk of human blood-borne viral contamination is essentially zero (15). Recombinant factor IX is considered to be the treatment of choice for patients with hemophilia B. (Table IIA)

2. Plasma-Derived Factor IX Concentrates

Improved viral depleting processes and donor screening practices have resulted in plasma-derived FIX products with greatly reduced risk for HIV, HBV, and HCV transmission (16). Viral attenuation methods used in the production of licensed FIX 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 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 has been documented, but the risk has been reduced with additional viral attenuation methods. (Table IIB)

3. Reduction of Thromboembolic Risk During Surgery

The use of recombinant factor IX or coagulation FIX concentrates rather than prothrombin complex concentrates is recommended in certain situations associated with a higher risk of thromboembolic complications such as surgery or severe hemorrhage requiring treatment 1 to 2 times per day.

C. Treatment of von Willebrand Disease (VWD)

1. Desmopressin

Most persons with von Willebrand disease type 1 are most appropriately 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. (Table IV)

2. VWF-Containing Factor VIII Concentrates

If judged necessary e.g., Type 2B VWD, Type 3 VWD, and Type 1 or 2A VWD who have become transiently unresponsive to DDAVP, and in surgical situations, especially in young patients, use of a viral-inactivated FVIII preparation rich in von Willebrand factor is recommended (17-21). Humate-P has been licensed by the FDA for use in von Willebrand disease; in certain patients Alphanate or Koate-DVI may also be effective. (Table IC)

3. Cryoprecipitate Not Recommended

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

D. Treatment of Patients with Inhibitors to Factors VIII and IX

The following products have been licensed for use in patients with inhibitors. However, the products are not interchangeable. Choice of product depends on multiple factors, including type of inhibitor (low- or high-responding), current titer of the inhibitor, location of the bleed, and availability of these products.

1. Activated Prothrombin Complex Concentrates

These products contain 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. These products are derived from human plasma and are treated with dry heat and/or vapor (steam) heat to eliminate viruses (22). (Table IID)

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 product). Thus the risk of transmission of human viruses is essentially zero (23). (Table III)

3. Porcine Factor VIII Concentrate

Porcine factor VIII can be used in patients with inhibitors to human factor VIII. Porcine factor

VIII is obtained from a colony of carefully maintained pigs that are screened frequently for several viruses. There has been no documented transmission of porcine viruses, especially porcine parvovirus, to individuals who have been treated with this product (24). (Table ID)

E. Treatment of Patients with Rare Congenital Bleeding Disorders

1. Although there is no product currently licensed to treat rare bleeding disorders, based on information available to NHF the following products are listed to enable healthcare providers to advise and treat these patients.

- 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).(23) It can be used to treat patients with congenital factor VII deficiency. (Table III)

- b. Prothrombin Complex Concentrates

Plasma-derived prothrombin complex concentrates (PCCs) can be used to treat patients with deficiencies of factors II, VII, 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.(22) (Table IIC)

- c. Fibrogammin P is a plasma-derived factor XIII concentrate for treatment of factor XIII deficiency. It is not yet licensed in the United States but is available under an Investigational New Drug (IND) protocol.

2. 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 mild 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.(25) This product is available from some community blood centers. (Table V)

- b. Cryoprecipitate is the currently recommended product for factor XIII deficiency, afibrinogenemia, and dysfibrinogenemia. It has not been treated to reduce viral transmission.

F. Vaccination for Hepatitis A and B

1. Hepatitis B vaccine is recommended for all children by the American Academy of Pediatrics. 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. Primary immune response should be documented.

2. Hepatitis A vaccine is recommended for all individuals 2 years of age and older with hemophilia and other congenital bleeding disorders who are HAV seronegative. (26-27)

G. 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. If a previously seronegative patient seroconverts to any blood-borne virus, this should be immediately reported to the FDA, to the manufacturer of the product received, and to the CDC.
2. MASAC recommends continued viral safety studies of all licensed products and continued maintenance of the CDC UDC serum bank to enable quick evaluation of possible transmission of viral infection by such products.
3. 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.
4. Patients should enroll in a voluntary 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. Plasma must not be collected from 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 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 and processed by fractionators certified by the QSEAL program of the Plasma Protein Therapeutics Association 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 at risk for CJD 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, and if marketed, withdrawn.
- 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 CJD.

1. Tests to identify viral nucleic acids (e.g., polymerase chain reaction [PCR] and other genome amplification tests) should be implemented expeditiously for all plasma that will be further processed.
 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), should offer 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 CJD and VCJD should be given high priority.
- C. Plasma pools should be decreased in size 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 further exposure to donors.
 4. Reduction in the number of donors in final lots of product will decrease the amount of product withdrawn or quarantined as a result of identification of a donor with a potentially transmittable disease (e.g., CJD, VCJD).
- D. Improved viral inactivation and elimination 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. New methods must be identified to minimize the chance of transmitting new agents which may emerge in the blood supply.
 4. Research to identify methods to eliminate the infectivity of the CJD agent and similar prion agents that may appear in the blood supply (e.g., variant CJD) is urgently needed.
- 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 the specific manufacturing practices.
- 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 with small numbers of patients evaluated in clinical trials. Manufacturers are strongly encouraged to conduct Phase IV post-licensure studies for efficacy and surveillance for viral infections.
 4. The FDA is bringing 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 enhanced training programs, manufacturing controls, quality assurance, and quality control and proactively take necessary steps to bring their facilities into compliance, if they have not already done so.
- 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 customers. The FDA has defined the customer as the “end-user” of the product: namely, the 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 notification system implemented by some companies will go a long way toward putting a system into place, it should not be considered a substitute for the responsibility the manufacturers have to notify their customers directly.
 4. Intermediaries, including home care companies, 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 and improved products to treat patients with von Willebrand disease and patients with inhibitors are urgently needed.
 2. Recombinant products that could be taken less frequently or administered other than intravenously would be of tremendous benefit to individuals on prophylaxis regimens.
 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.

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. 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 at plasma collection centers, and establishment of sensitive genome amplification tests.
- B. The FDA should implement pool size restrictions along the lines of their proposal in 1996 of 15,000 donors for source plasma.
- C. Research to identify improved inactivation and elimination techniques for non-lipid enveloped viruses should be actively encouraged by the FDA.
- D. Validation studies to identify the amount of removal of the CJD agent should be recommended by the FDA to each manufacturer for each of their products.
- E. 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 all CJD-related agents.
- F. The FDA should maintain sufficient compliance checks to ensure that manufacturers are expeditiously reporting any and all suspected infectious agents associated with coagulation products.
- G. 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.
- H. 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.
- I. The FDA has the authority to regulate a mandatory notification system that follows the product through its entire distribution pathway. The FDA should enforce the implementation and maintenance of such a system.
- J. The FDA should continue to bring the coagulation products industry in line with good manufacturing practices of pharmaceutical companies that manufacture other classes of drugs.
- K. All products offering incremental safety and efficacy advantages to the bleeding disorders community should have expedited regulatory review.
- L. The FDA should communicate promptly with consumer organizations such as NHF whenever an event occurs, such as a recall or withdrawal or a consent decree or plant closure, which could have an impact on the supply and availability of clotting factor concentrates.

REFERENCES

1. Bray GL, Gomperts ED, Courter S, et al. A multicenter study of recombinant factor VIII (Recombinate): safety, efficacy and inhibitor risk in previously untreated patients with hemophilia A. Blood 1994; 83:2428-2435.
2. Lusher JM, Arkin S, Abildgaard CF, Schwartz RS, Group TKPUPS. Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A. N Engl J Med 1993; 328:453-459.
3. Sandberg H, Almstedt A, Brandt J, et al. Structural and functional characteristics of the B-domain-deleted recombinant factor VIII protein, r-VIII SQ. Thromb Haemostas. 2001; 85:93-100.
4. Horowitz MS, Horowitz B, Rooks C, Hilgartner MW: Virus safety of solvent/detergent-treated antihaemophilic factor concentrate. Lancet 1988; 2:186-188.
5. Schimpf K, Mannucci PM, Kreutz W, et al. Absence of hepatitis after treatment with a pasteurized factor VIII concentrate in patients with hemophilia and no previous transfusions. N Engl J Med 1987; 316:918-922.
6. Addiego JE, Jr., Gomperts E, Liu S-L, et al: Treatment of hemophilia A with a highly purified factor VIII concentrate prepared by anti-FVIII immunoaffinity chromatography. Thromb Haemostas 1992; 67:19-27.
7. Mannucci PM, Gdovin S, Gringeri A, et al. Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with solvent and detergent to inactivate viruses. Ann Int Med 1994; 120:1-7.
8. Centers for Disease Control and Prevention. Hepatitis A among persons with hemophilia who received clotting factor concentrate - United States, September - December 1995. MMWR 1996; 45:29-32.
9. Azzi A, Ciappi S, Zakuyzewska K, et al. Human parvovirus B19 infection in hemophiliacs first infused with two high-purity, virally treated factor VIII concentrates. Am J Hematol 1992; 39:228-230.
10. de Biasi R, Rocine A, Quirino A, Miraglia E, Ziello L: The impact of a very high purity factor VIII concentrate on the immune system of HIV-infected haemophiliacs: a randomized, two year comparison with a high purity concentrate. Haemophilia 1996; 2:82-87.
11. Study Group of the UK Haemophilia Center Directors on Surveillance of Virus Transmission by Concentrates. Effect of dry heating of coagulation factor concentrates at 80°C for 72 hrs on transmission of non-A, non-B hepatitis. Lancet 1988; 2:184-186.
12. Shapiro A, Abe T, Aledort LM, Anderle K, et al: Low risk of viral infection after administration of vapor-heated factor VIII concentrate or factor IX complex in first-time recipients of blood components. Transfusion 1995; 35:204-208
13. Mannucci PM, Zanetti AR, Colombo M and the Study Group of the Fondazione dell' Emophilia: Prospective study of hepatitis after factor VIII concentrate exposed to hot vapour. Br J Haematol 1988; 68:427-430.

14. Dodd RY, Notari EP, Stamer SL. Current prevalence and incidence of infectious disease markers and estimated window period risk in the American Red Cross blood donor population. Transfusion 2002; 42:975-979.
15. White G, Shapiro A, Ragni M, Garzone P, Goodfellow J, Tubridy K, Courter S. Clinical evaluation of recombinant factor IX. Semin Hematol. 1998; 35 (Suppl. 2):33-38.
16. Shapiro AD, Ragni M, Lusher JM, Culbert S, Koerper MA, Bergman, GE, Hannan MM: Safety and efficacy of monoclonal antibody-purified factor IX in patients previously unexposed to PCC or other blood products. Thromb Haemostas 1996; 75:30-35.
17. Scharrer I: The treatment of von Willebrand's disease. In: Lusher JM and Kessler CM, eds: Hemophilia and von Willebrand's Disease in the 1990s. Elsevier Science Pulil B.V., Amsterdam, 1991; pp. 463-469.
18. Scharrer I, Vigh T, Aygoren-Pursun E: Experience with Haemate P in von Willebrand's disease in adults. Haemostasis 1994; 24:298-303.
19. Berntorp E: Plasma product treatment in various types of von Willebrand's disease. Haemostasis 1994; 24:289-297.
20. Mannucci PM: Biochemical characteristics of therapeutic plasma concentrates used in the treatment of von Willebrand's disease. Haemostasis 1994; 24:285-288.
21. Kreuz W, et al: Haemate P in children with von Willebrand's disease. Haemostasis 1994; 24:304-310.
22. Kasper CK, Lusher JM, and Transfusion Practices Committee, AABB: Recent evolution of clotting factor concentrates for hemophilia A and B. Transfusion 1993; 33:422-434.
23. Key NS, Aledort LM, Beardsley D, et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (NovoSeven) in haemophiliacs with inhibitors. Thromb Haemostas 1998; 80:912-918.
24. Morrison AE, Ludlam CA, Kessler C. Use of porcine factor VIII in the treatment of patients with acquired hemophilia. Blood 1993; 81:1513-1520.
25. Piet MP, Chin S, Prince AM, et al. The use of tri(n-butyl) phosphate detergent mixtures to inactivate hepatitis viruses and human immunodeficiency virus in plasma. Transfusion 1990; 30:591-598.
26. Ragni MV, Lusher JM, Koerper MA, Manco-Johnson M, Krouse DS. Safety and immunogenicity of subcutaneous hepatitis A vaccine in children with haemophilia. Haemophilia 2000; 6:98-103.
27. Andre FE, et al. Clinical assessment of the safety and efficacy of an inactivated hepatitis A vaccine: Rationale and summary of findings. Vaccine 1992; 10 (Suppl):S160-168.

GLOSSARY TO MASAC RECOMMENDATIONS

Activated Prothrombin Complex Concentrate

Two prothrombin complex concentrates are purposely "activated" so that they contain some FIX, FX in active form (FIXa, FXa). Autoplex T and FEIBA are to be used in inhibitor patients only.

Coagulation Factor IX Concentrate

Factor IX products which 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

No currently available FVIII products are exclusively dry heat-treated. The currently available FIX products that are dry heat-treated are Autoplex and Proplex-T, which are dry-heated at 60°C for 144 hours.

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. One product, Humate-P, has been approved by the FDA for use in patients with von Willebrand disease. Two other products, Alphanate and Koate-DVI, may also be effective in preventing or controlling bleeding in persons with VWD.

First Generation Recombinant Factor Concentrate

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

Heated in Aqueous Solution (Pasteurized)

Factor VIII concentrates that are heated for 10 hours at 60°C in aqueous solution in the presence of stabilizers such as sucrose or neutral amino acids include Humate-P and Monoclate P.

Immunoaffinity Purified

Factor VIII or FIX concentrates that are purified using murine monoclonal antibodies attached to an affinity matrix. Viral attenuation is augmented before immunoaffinity purification by pasteurization (Monoclate P) or by solvent/detergent treatment (Hemofil M and Monarc-M). In the case of Mononine (a coagulation FIX

product), viral attenuation is augmented by sodium thiocyanate and ultrafiltration.

Prothrombin Complex Concentrate

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 VH, Profilnine SD, and Proplex-T.

Recombinant Factor Concentrate

Recombinant (r) factor concentrate refers to genetically engineered concentrate that is not derived from human or animal plasma. 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. Another rFVIII product, ReFacto, lacks the B domain of FVIII. The rFVIII is produced by Chinese hamster ovary cells.

A recombinant FIX product, BeneFIX, is produced by Chinese hamster ovary cells.

A recombinant FVIIa product, NovoSeven, is produced by baby hamster kidney cells. It is used to treat patients with inhibitors to factors VIII and IX.

Second Generation Recombinant Factor Concentrate

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

Solvent Detergent Treated

Factor VIII concentrates 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). Alphanate and Koate-DVI are solvent-detergent treated using TNBP and Polysorbate 80. Hemofil M and Monarc-M are solvent-detergent treated with TNBP and Triton X-100. A coagulation FIX product (AlphaNine SD) is solvent-detergent treated using TNBP and Polysorbate 80, as is the prothrombin complex concentrate Profilnine SD.

Third Generation Recombinant Factor Concentrate

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

Vapor Treated

Two coagulation products currently licensed in the U.S. use vapor (steam) treatment for viral attenuation. Bebulin VH, a prothrombin complex concentrate, and FEIBA VH, 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.