MASAC RECOMMENDATIONS CONCERNING PRODUCTS LICENSED FOR THE TREATMENT OF HEMOPHILIA AND OTHER BLEEDING DISORDERS
(Revised April 2018)

The document was approved by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) on April 19, 2018 and adopted by the NHF Board of Directors on April 23, 2018.

This material is provided for your general information only. NHF does not give medical advice or engage in the practice of medicine. NHF under no circumstances recommends particular treatment for specific individuals and in all cases recommends that you consult your physician or local treatment center before pursuing any course of treatment.

Copyright 2018 National Hemophilia Foundation. To facilitate the dissemination of these medical recommendations, reproduction of any material in this publication in whole or in part will be permitted provided: 1) a specific reference to the MASAC recommendation number and title is included and 2) the reproduction is not intended for use in connection with the marketing, sale or promotion of any product or service. NHF reserves the right to make the final determination of compliance with this policy. For questions or to obtain a copy of the most recent recommendations, please contact the NHF Director of Communications at 1-800-42-HANDI or visit the NHF website at www.hemophilia.org.
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 often 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 (F8). (1, 2) Two newer rFVIII products are
produced in human embryonic kidney (HEK) cell lines. In some products, the rFVIII is
full length, while in other products the B-domain is largely deleted. Either 14 amino
acids (Xyntha, Eloctate), 16 amino acids (Nuwiq), or 21 amino acids (NovoEight) of the
B-domain remain in the rFVIII. (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-derived proteins in the culture medium but not in the final
formulation vial. Third generation rFVIII does not contain any animal or human
plasma-derived proteins in the culture medium or in the final formulation vial.

   A new third generation recombinant Factor VIII product fused to the Fc fragment of
human IgG (rFVIIIFe), inhibits lysosomal degradation of rFVIII by reticuloendothelial
cells, thus prolonging FVIII half-life in the circulation. There are no human or animal
proteins employed in its production.

   A third new-generation recombinant FVIII product is produced in Chinese Hamster
Ovary cells (CHO) cells. It is PEGylated to delay degradation and thereby prolong its
half-life. There are no human or animal proteins employed in its production.

   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 rFVIII products.
Recombinant factor VIII products are the recommended treatment of choice for patients
with hemophilia A. (33) (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 dry-heated, 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 to older methods of viral inactivation (4-6).

   There remains the slight possibility of HIV 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
previously transmitted by pdFVIII (7-9); however, additional steps such as
nanofiltration have been added to the manufacturing process to reduce risks of these viral infections as well. (Table I.B., Table I.C.)

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 (dry heat, 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).

Despite donor screening by nucleic acid testing (NAT) for HIV, 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)

For these reasons, cryoprecipitate, which has not had any viral elimination steps applied, should not be used as a treatment alternative for hemophilia A unless there is a risk to loss of life or limb and no FVIII concentrate is available.

4. 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 significant rise in FVIII. DDAVP is available in both a parenteral form (DDAVP Injection) and a highly concentrated intranasal spray formulation (Stimate Nasal Spray for Bleeding). (14) (Table I.D.)

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

Desmopressin should be used with caution in pregnant women during labor and delivery. (15)
In all patients, careful attention should be paid to fluid restriction, since excessive water intake can lead to hyponatremia and seizures.

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 or in the final formulation vial (third generation product). Thus, the risk of human blood-borne viral contamination is much lower than for plasma-derived factor IX concentrates. (16)

New third generation recombinant Factor IX products are fused with either the Fc fragment of human IgG (rFIXFc) or with albumin (rFIX-FP), both of which inhibit lysosomal degradation of rFIX by endothelial cells. One is conjugated with PEG (N9-GP) to reduce clearance, thus prolonging the half-life of rFIX in the circulation. rFIXFc is produced in a human embryonic kidney (HEK) cell line (32), while rFIX-FP and N9-
GP are produced in CHO cells (36). There are no human or animal proteins employed in the cell culture or in the final formulation vial (third generation recombinant product). (32)

Recombinant factor IX products are the recommended 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 (17). 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 the addition of viral attenuation methods such as nanofiltration. (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 for Bleeding). Some Type 2A patients may respond to DDAVP; a DDAVP trial should be done to determine whether DDAVP can be used for these patients. (14) (Table III.A.)

Desmopressin should not be used in certain categories of patients:
1. Children under the age of 2 years and
2. Patients with von Willebrand disease in whom desmopressin does not provide adequate von Willebrand factor levels

These patients should be treated as per section I.C.2 or I.C.3 above.

Desmopressin should be used with caution in pregnant women during labor and delivery. (15) (Table III.A.)

In all patients, careful attention should be paid to fluid restriction, since excessive water intake can lead to hyponatremia and seizures.

2. Recombinant VWF concentrate
A recombinant VWF concentrate is available to treat patients with type 2B and type 3 VWD; it can also be used in patients with types 1, 2A, 2M, and 2N VWD who are not responsive to DDAVP and in children under 2 years of age regardless of VWD type. It is produced in Chinese Hamster Ovary (CHO) cells; there are no human or animal-derived proteins used in its cell culture or in the final formulation vial (third generation...
rVWF). It contains ultra-large VWF multimers in addition to the high, medium and low molecular weight VWF multimers normally found in plasma. There are trace amounts of rFVIII in the product as well. (35)

Recombinant products are the treatment of choice for patients with inherited bleeding disorders. (Table III.B.)

3. Plasma-derived VWF-Containing Factor VIII Concentrates
Certain viral-inactivated pdFVIII concentrates that are rich in von Willebrand factor may be used in patients with certain types of VWD who do not respond to DDAVP, i.e. Type 2B VWD and Type 3 VWD, and also in patients with Types 1, 2A, 2M and 2N VWD who have become transiently unresponsive to DDAVP, as well as in surgical situations, especially in young children under the age of 2 years. (18-22) (Table III.C.)

4. Cryoprecipitate Not Recommended for VWD
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 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 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 (ITI) is the best option for inhibitor eradication. Consultation with a Hemophilia Treatment Center is strongly recommended. (24)

1. Bypassing Agents (BPA) for hemophilia A or B with inhibitors
   a. 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 (24). (Table IV.A.)
   b. NovoSeven RT (Recombinant Activated Factor VII Concentrate)
      Recombinant activated factor VII (rFVIIa) 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 (BHK) cells; newborn calf serum is used in the culture medium; no human or other animal proteins are used in its final formulation vial (second generation recombinant product). Thus, the risk of transmission of human viruses is essentially zero (25). (Table IV.B.)

2. Bispecific antibody for hemophilia A with inhibitors
   a. HEMLIBRA (emicizumab-kxwh)
      Hemlibra is a humanized bispecific FIXa- and FX- directed monoclonal antibody
that bridges between FIXa and FX, thereby bypassing the FVIII inhibitor to prevent or reduce bleeding in patients with hemophilia A and inhibitors. (37) Table IV.C.)

3. **Thromboembolic Risk**
   Thrombotic risks exist with the use of all 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 VII (rhFVIIa) that is produced in Baby Hamster Kidney (BHK) cells. It is licensed for use 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 F8 gene. This is a second-generation recombinant product that is approved by the FDA for use only 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. (34) (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 hypo-fibrinogenemia and afibrinogenemia but not dysfibrinogenemia. (26) (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 VII Concentrate**
         Recombinant activated factor VII (rFVIIa) can be used to treat patients with congenital factor VII deficiency. It is produced by baby hamster kidney (BHK) cells. Newborn calf serum is used in the culture medium; no human or other animal protein is used in the final formulation vial (second generation recombinant product). Thus, the risk of transmission of human viruses is essentially zero. (25) (Table VI.B.)
3. **Factor X deficiency**  
   a. **Plasma-derived Factor X Concentrate**  
      Factor X concentrate is a plasma-derived concentrate approved in the US for treatment of Factor X deficiency. It has three viral attenuation steps: solvent/detergent, nanofiltration, and dry heat at 80° for 72 hours. (Table VI.C.)

4. **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 for viral inactivation and removal. It can be used for patients with absent or decreased levels of FXIII. (27) (Table VI.D.)  
   b. **Recombinant Factor XIII-A Subunit Concentrate**  
      Recombinant Factor XIII-A subunit (rFXIII-A) concentrate is produced in yeast. No human or animal-derived proteins are used in the production vat or in the final formulation vial (third generation recombinant concentrate). This product is approved for use in individuals who lack FXIII-A subunit. It will not work in those patients who only lack FXIII-B subunit. (28) (Table VI.E.)  
   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.)

5. **Other Rare Bleeding Disorders:**  
   Although there are no products currently licensed to treat other rare bleeding disorders, the following products are listed to enable healthcare providers to advise and treat these patients.

   **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 two different commercial preparations, but factor content varies among lots produced by the same manufacturer. (29) (Table VI.F.)

6. **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 concentrate that is subjected to pasteurization and nanofiltration as viral attenuation methods. (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.)

7. The following blood components may be used to treat 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. It is 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 dose 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). It can also be given IV following oral (e.g. wisdom tooth extraction) or ENT (e.g. tonsillectomy) surgery (Table IX.A.)

   b. Tranexamic acid (Lysteda) is an oral antifibrinolytic agent that is approved for treatment of 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 any 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 hemophilia 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. (30-31)

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 reported immediately 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 utilizing Plasma Protein Therapeutics Association (PPTA) guidelines and recommendations.

2. 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.

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 poorly inactivated by current viral elimination techniques, namely, HAV and parvovirus B19.
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.

   2. Research to identify methods to eliminate should be given higher priority.

E. Reporting of adverse events associated with coagulation products should occur more expeditiously.
   1. Manufacturers should report suspected viral transmission events to the FDA immediately upon confirmation.

   2. 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. Recombinant products should continue to be developed that could be taken less frequently and administered by routes other than intravenously.

   2. As improvements in production efficiencies are made, cost reductions of coagulation products should be passed on to the consumer.

   3. Biosimilar FVIII and FIX products are now available and should be a vehicle for substantial cost reductions, as they are in all other therapeutic areas.
4. Inhibitor development is the single most important complication of treatment of Hemophilia A and B. BioPharma should apply their resources toward technologies which would limit the development of this complication.

5. BioPharma should facilitate the clinical development of gene therapies to cure bleeding disorders.

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.

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.

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. This includes experimental gene therapies.
2. The FDA should work with the EMA 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,

3. PUP trials of single agents should not be required, and should be discouraged in favor of interventional trials designed to decrease rates of inhibitor formation.
REFERENCES


17. 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.
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.

B-domain-deleted recombinant Factor VIII concentrates
For some rFVIII concentrates, the F8 gene that is inserted into a hamster or human cell line that will produce recombinant FVIII that has the B domain of FVIII deleted. The result is production of a smaller FVIII molecule, thus enhancing production in the bioreactor.

Bioengineered Recombinant Factor Concentrates
Some rFVIII concentrates have been bioengineered to modulate functional properties of the molecule. This includes strategies which alter the pharmacokinetic properties of the molecule. For example, 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 partner protein to the gene for factor VIII or IX before the factor gene is inserted into a cell line for production of the recombinant factor-fusion protein molecule. The purpose of adding the fusion protein is to prolong the half-life of the infused factor in the circulation. Another approach to prolonging half-life is to conjugate the factor protein to another molecule such as PolyEthylene Glycol (PEG) which delays degradation of the factor, thus prolonging the half-life in the circulation.

Bispecific Antibody
A humanized bispecific monoclonal antibody that binds to FIXa and FX to bypass a FVIII inhibitor to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A and FVIII inhibitor. (Table IV.C.)

Bypassing Agent (BPA)
Two coagulation products can be used to bypass a FVIII or a FIX inhibitor in patients with inherited hemophilia A or B. One is plasma-derived and the other is a recombinant product. They must be used with care and with consultation with an HTC because of a thrombotic risk. (Table IV.A. and B.)

Coagulation Factor IX Concentrates
These are plasma-derived Factor IX concentrates that contain very little or no coagulation factors other than FIX.

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.

Dry Heat-treated Concentrates
No currently available FVIII or FII 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 plasma-derived FVIII concentrates, the hemostatically important high molecular weight multimers of von Willebrand factor are preserved.

**First Generation Recombinant Factor Concentrates**
Animal and/or human proteins are used in the cell culture medium and in the final formulation vial of these concentrates.

**Immuoaffinity 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, by solvent/detergent treatment, or by sodium thiocyanate and ultrafiltration.

**Intermediate Purity Factor Concentrates**
Plasma-derived factor concentrates that contain several clotting factors and plasma proteins in addition to the assayed factor.

**Pasteurized Factor Concentrates (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 in order to inactivate viruses.

**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.

**Recombinant Factor Concentrates (rF)**
Recombinant factor concentrate refers to a genetically engineered concentrate that is not derived from human or animal plasma. The gene encoding normal human FVIII is inserted into a hamster cell [cells obtained from well-established baby hamster kidney (BHK) cell lines or Chinese Hamster Ovary (CHO) cells] or else a human cell line [human embryonic kidney (HEK)]. The transfected cells then produce rFVIII that is indistinguishable from plasma-derived human FVIII. Recombinant FIX products are produced by CHO cells or HEK cells. A recombinant VWF concentrate is produced by CHO cells, while a recombinant FVIIa product is produced by BHK cells. A recombinant FXIII-A subunit product, produced in yeast, is available to treat patients with FXIII-A subunit 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.

**Second Generation Recombinant Factor Concentrates**
Animal and/or human proteins are used in the cell culture medium but not in the final formulation vial of these concentrates.
**Solvent Detergent Treated Concentrates**
Plasma-derived factor concentrates that are manufactured using combinations of a solvent, with a detergent, to inactivate lipid-enveloped viral contaminants (lipid-enveloped viruses include HIV, HBV, HCV).

**Third Generation Recombinant Factor Concentrates**
No animal or human protein is used in the cell culture medium or in the final formulation vial of these products. The product is stabilized with a sugar such as sucrose or trehalose.

**Vapor-treated Concentrates**
Two plasma-derived coagulation products currently licensed in the U.S. use vapor (steam) treatment for viral attenuation. They are vapor treated for 10 hours at 60°C and 190 mbar pressure, followed by 1 hour at 80°C under 375 mbar pressure.