



NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Document #259
(Replaces Document #253)

**MASAC RECOMMENDATIONS CONCERNING PRODUCTS LICENSED FOR THE
TREATMENT OF HEMOPHILIA AND OTHER BLEEDING DISORDERS**
(Revised February 2020)

*The document was approved by the Medical and Scientific Advisory Council (MASAC) of
the National Hemophilia Foundation (NHF) on February 28, 2020, and adopted by the NHF
Board of Directors on _____.*

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 2020 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 Healthcare Providers and 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.

One third generation recombinant Factor VIII product that is fused to the Fc fragment of human IgG (rFVIIIFc) 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. (4)

Another third generation recombinant FVIII product, produced in CHO cells, 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 exceedingly low. No seroconversions to human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (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. A possible exception to this recommendation is a newly diagnosed individual, who should also consider with their healthcare providers initiating treatment with a plasma-derived factor VIII / von Willebrand Factor (VWF) product (see MASAC Recommendation on SIPPET, Document #243). ([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 HIV, HBV, and HCV. 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 (5-7).

There remains the slight possibility of HIV, HBV, or HCV 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 (8-10); 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. Bispecific Antibody for Hemophilia A

a. Hemlibra (emicizumab-kxwh)

Emicizumab is a humanized, bispecific, monoclonal antibody that binds to FIX / FIXa and FX / FXa, thereby standing in for the missing FVIII to prevent or reduce the occurrence of bleeding in patients with hemophilia A. It was shown in phase 3 clinical trials to be safe and effective in adults, adolescents, children, and infants with hemophilia A with and without inhibitors (11-13). Subcutaneous administration of emicizumab is often viewed as being easier and/or less time consuming compared to intravenous administration of FVIII. Dosing intervals are also much longer than FVIII, with prophylaxis regimens for emicizumab with weekly, every 2 weeks, or every 4 weeks dosing. In those undergoing major surgery, preliminary experience suggests standard preoperative dose FVIII and tapering postoperative doses may be safe and effective, while in some minor surgeries, low or no FVIII may be appropriate. (14) ([Table IV.C.](#))

4. Cryoprecipitate Not Recommended for Hemophilia A

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, HBV and HCV transmission with plasma-derived factor VIII concentrates (6-7, 15-17).

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. (18)

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.

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 clinically 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). (19) ([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 FVIII levels for the specific intended treatment purpose.

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.
(20)

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 Concentrates

Recombinant factor IX (rFIX) is produced in CHO or HEK 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. (21)

New third generation rFIX 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. Another product is conjugated with PEG (N9-GP) to reduce clearance, thus prolonging the half-life of rFIX in the circulation. rFIXFc is produced in an HEK cell line (22), while rFIX-FP and N9-GP are produced in CHO cells (23). There are no human or animal proteins employed in the cell culture or in the final formulation vial (third generation recombinant product). (22)

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 (24). 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 VWD type 1 may be treated with desmopressin, given either parenterally (DDAVP Injection) or by highly concentrated nasal spray (Stimate Nasal Spray for Bleeding). Some VWD Type 2A patients may respond to DDAVP; a DDAVP trial should be done to determine whether DDAVP can be used for these patients. (19) ([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 VWD in whom desmopressin does not provide adequate VWF levels for the specific intended treatment purpose.

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

Desmopressin should be used with caution in pregnant women during labor and delivery. (20) ([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

Recombinant VWF (rVWF) 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 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. (25)

3. Plasma-Derived VWF-Containing Factor VIII Concentrates

Certain viral-inactivated pdFVIII concentrates that are rich in VWF 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, and especially in young children under the age of 2 years. (26-30) ([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 and/or prevention 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. (31)

1. Bypassing Agents (BPA) for Hemophilia A or B with Inhibitors

a. FEIBA (Activated Prothrombin Complex Concentrate [aPCC])

FEIBA contains activated factors IIa, VIIa, IXa 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 (32). ([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 in 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 (33). ([Table IV.B.](#))

2. Bispecific Antibody for Hemophilia A with Inhibitors

a. Hemlibra (emicizumab-kxwh)

Emicizumab is a humanized, bispecific, monoclonal antibody that binds to FIX / FIXa and FX / FXa, thereby standing in for the missing FVIII to prevent or reduce the occurrence of bleeding in adults, adolescents, children and infants with hemophilia A and inhibitors (34, 13). In those undergoing major surgery, preliminary experience suggests standard preoperative dose rFVIIa and tapering postoperative doses may be safe and effective, while in some minor surgeries, low or no rFVIIa may be appropriate (14). ([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. In particular, in those using emicizumab prophylaxis, concomitant FEIBA should be avoided during and up to six months after emicizumab use, as residual emicizumab levels may persist in the plasma (MASAC Document #255).

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, systemic lupus erythematosus, and other autoimmune disorders. Often no associated condition can be identified. Individuals with acquired hemophilia A 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 factor VII (rFVIIa) that is produced in 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. (35) ([Table V.A.](#))
3. FEIBA (aPCC) contains activated factors IIa, VIIa, IXa 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 (32). ([Table IV.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. (36) ([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 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. (33) ([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. (37) ([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. (38) ([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.

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 two different commercial preparations, but factor content varies among lots produced by the same manufacturer. (39) ([Table VI.F.](#))

b. Fresh Frozen Plasma (FFP)

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.](#))

G. Treatment of Patients with Rare Congenital Clotting Disorders

1. Antithrombin Deficiency

There are two products available for treatment of Antithrombin deficiency:

- a. 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.](#))
- b. The second product is a plasma-derived human Antithrombin concentrate that is subjected to pasteurization and nanofiltration as viral attenuation methods. ([Table VII.A.](#))

2. Protein C Deficiency

There is 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.](#))

H. Ancillary Medications

1. Vitamin K. Newborn infants with hemophilia and other bleeding disorders should be given an intramuscular dose of Vitamin K in the delivery room per the recommendations of the American Academy of Pediatrics. For infants who are known or suspected to have a bleeding disorder, we recommend that the following procedures be followed for intramuscular administration of vitamin K (see MASAC Document #221):
 - a. A fine-gauge needle (23 gauge or smaller caliber) should be used.
 - b. Firm pressure should be applied to the site for at least 2 minutes without rubbing.
 - c. The parent / caregiver should be informed that there is a risk of hematoma development at the injection site.
 - d. Anticipatory guidance should be given regarding when to call the provider or HTC regarding any adverse reactions, such as hematoma, warmth, or redness.
2. Antifibrinolytics
 - a. Amicar (aminocaproic acid) is an antifibrinolytic agent that can be used to treat mouth and other mucosal bleeds. It comes as a syrup with a concentration of 1.25 g/5ml or in pill form. 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. Lysteda (tranexamic acid) is an antifibrinolytic agent that is approved for treatment of heavy menstrual bleeding in females \geq 12 years of age. 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. Unless recommended by one of their medical providers in consultation with their treating hematologist or hematology provider, individuals with inherited bleeding disorders should not use anti-platelet medications or non-selective non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen, naproxen and others).

Although NSAID use should generally be discouraged in individuals with bleeding disorders, these medications may be used to provide analgesia in some patients, particularly those with chronic joint pain who prefer or need to avoid or minimize the use of opioid medications. If using NSAIDs to treat pain, we recommend using the lowest effective dose for short durations only, given the risk of gastrointestinal (GI) ulcer formation and significant GI bleeding when NSAIDs are used continuously. Patients should also be monitored for increases in the frequency or severity of joint bleeds or other types of bleeding if they use NSAIDs for pain exacerbations.

I. 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. (40-41)

J. 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 infectious pathogens should be given higher priority.
- D. 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.
- E. 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.
- F. 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.
- G. 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 U.S. 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 European Medicines Agency (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. Previously untreated patient (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

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. Mahlangu J, J Powell, M Ragni, et al. Phase 3 study of recombinant factor VIII Fc in hemophilia A. *Blood* 2014; 124:317-325.
5. Horowitz MS, Horowitz B, Rooks C, Hilgartner MW. Virus safety of solvent/detergent-treated antihaemophilic factor concentrate. *Lancet* 1988; 2:186-188.
6. 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.
7. 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.
8. Mannucci PM, Godovin 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.
9. 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.
10. 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: 228-30.
11. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in hemophilia A without inhibitors. *N Engl J Med* 2018; 379; 811-22.
12. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with Haemophilia A (HAVEN 4): a multi-center open-label, non-randomised phase 3 study. *Lancet Hematol* 2019; 6: e295-e305.
13. Batsuli G, Zimowski KL, Tickle K, Meeks SL, Sidonio RF. Immune tolerance induction in paediatric patients with haemophilia A and inhibitors receiving emicizumab prophylaxis. *J Thromb Haemost* 2019; 25: 789-796.
14. Ebbert P, Xavier F, Seaman C, Ragni MV. Emicizumab prophylaxis in patients with hemophilia A with and without inhibitors. 2019 American Society of Hematology Annual Meeting, Orlando, FL. Abstract #2416.
15. 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 hours on transmission of non-A, non-B hepatitis. *Lancet* 1988; 2:184-186.

16. 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.
17. 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.
18. 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.
19. Rose EH, Aledort LM. Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease. *Ann Intern Med* 1991; 114: 563-8.
20. Trigg DE, Stergiotou I, Peitsidis P, Kadir RA. A systematic review: The use of desmopressin for treatment and prophylaxis of bleeding disorders in pregnancy. *Haemophilia* 2012; 18: 25-33.
21. White G, Shapiro A, Ragni M, Garzone P, Goodfellow J, Tubridy K, Courier S. Clinical evaluation of recombinant factor IX. *Semin Hematol*. 1998; 35 (Suppl. 2):33-38.
22. Powell JS, Pasi KJ, Ragni MV et al. Phase 3 study of recombinant Factor IX Fc fusion protein in hemophilia B. *New Engl J Med* 2013; 369(24): 2413-24.
23. Schulte S. Half-life extension through albumin fusion technologies, *Thromb Res*, 2009, Dec; 124 Suppl 2: S6-8.
24. 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.
25. Gill J, Castaman G, Windyga J, Kouides P, Ragni M, Leebeek F, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in patients with severe von Willebrand disease. *Blood* 2015; 126: 2038-46.
26. Scharrer I. The treatment of von Willebrand disease. In: Lusher JM and Kessler CM, eds. *Hemophilia and von Willebrand Disease in the 1990s*. Elsevier Science Pulil B.V., Amsterdam, 1991; pp. 463-9.
27. Scharrer I, Vigh T, Aygoren-Pursun E. Experience with Haemate P in von Willebrand disease in adults. *Haemostasis* 1994; 24:298-303.
28. Berntorp E. Plasma product treatment in various types of von Willebrand disease. *Haemostasis* 1994; 24:289-297.
29. Mannucci PM. Biochemical characteristics of therapeutic plasma concentrates used in the treatment of von Willebrand disease. *Haemostasis* 1994; 24:285-288.
30. Kreuz W, et al. Haemate P in children with von Willebrand disease. *Haemostasis* 1994; 24:304-310.
31. Kempton CL, White II GC. How we treat hemophilia A patient with a factor VIII inhibitor. *Blood* 2009; 113: 11-17.
32. Stine KC, Shrum D, Becton DL. Use of FEIBA for invasive or surgical procedures in patients with severe hemophilia A or B with inhibitors. *J Pediatr Hematol Oncol*. 2007; 29: 216-21.
33. 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 Haemostasis* 1998; 80:912-918.

34. Oldenberg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *New Engl J Med* 2017; 377: 809-18.
35. Kruse-Jarres R, St-Louis J, Greist A, Shapiro A, Smith H, Chowdary P, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. *Haemophilia* 2015; 21(2):162-70. doi: 10.1111/hae.12627. Epub 2015 Jan 27.
36. Kreuz W, Meili E et al. Efficacy and tolerability of a pasteurised human fibrinogen concentrate in patients with congenital fibrinogen deficiency. *Transfus Apher Sci* 2005; 32: 247-53.
37. Hsieh L, Nugent D. Factor XIII deficiency. *Haemophilia* 2008; 14: 1190-2000.
38. Inbal A. et al. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. *Blood* 2012; 119(22): 5111-7.
39. Kasper CK, Lusher JM, and Transfusion Practices Committee, AABB. Recent evolution of clotting factor concentrates for hemophilia A and B. *Transfusion* 1993; 33:422-34.
40. 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.
41. 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):S160-8.

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 FIX concentrates are exclusively dry heat-treated. However, dry heat treating may be used in conjunction with other viral attenuation modalities.

Factor VIII Concentrates Rich in von Willebrand Factor

In certain 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.

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, 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.