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GUIDELINES

Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders

UNITED KINGDOM HAEMOPHILIA CENTRE DIRECTORS ORGANISATION EXECUTIVE COMMITTEE

1. Introduction

Since the previous recommendations were published in 1992 there have been significant developments in coagulation factor concentrates for treating haemophilia and other hereditary coagulopathies. Some of the products recommended in the previous recommendations are now no longer available and new high-purity and recombinant concentrates have become licensed. The trend continues to manufacture plasma-derived concentrates of higher purity, including some with two viral inactivation steps. Recombinant concentrates are now in widespread use and new recombinant products are under clinical trial. The United Kingdom Haemophilia Centre Directors Organization (UKHCDO) has therefore prepared these substantially revised guidelines which replace the previous recommendations [1]. The recommendations are consistent with those prepared under the auspices of the World Health Organization [2], National Haemophilia Foundation (USA) [3] and other European countries [4].

These guidelines offer advice on the choice of therapeutic products and are based on the best published scientific and medical information. They will be reviewed regularly by the Executive. Recently the UKHCDO has also prepared other guidelines on the treatment of various aspects of haemophilia and these are listed in Appendix 1.

Currently unlicensed coagulation factor concentrates may become licensed in the near future and these guidelines have therefore also included products available at present only in formal clinical trials or on a 'named patient basis'. As treatment is expensive it is important to ensure that limited resources are used optimally whilst not compromising safety. Guidance is given as to which of the recommendations should be current practice and which can be enacted when resources allow. To ensure that treatment arrangements are appropriate clinical audits should be a regular feature of all Haemophilia Centre activities; suggestions for this are given in these guidelines.

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2. Methods

The guidelines were drafted by a Task Force appointed by the UKHCDO Executive Committee and circulated widely for consultation. Relevant scientific papers were identified from Medline using the index terms h(a)emophilia, therapy, hepatitis, HIV, parvovirus, Creutzfeld–Jakob disease, immune and thrombosis [5]. Recommendations have been based on reports with the highest levels of evidence (Appendix 2). Members of the Task Force made a declaration of interest to the former Chairman, UKHCDO.

3. Manufacture of therapeutic coagulation factor concentrates (Tables 1–5)

3.1.1.1. Fresh plasma products

None of these products are currently virally inactivated.

3.1.1.2. Fresh frozen plasma (FFP). This is prepared from whole blood by cold centrifugation; the plasma is rapidly frozen in a liquid nitrogen, or mechanical, freezer.

3.1.1.3. Cryoprecipitate. This is prepared from FFP by slow thaw over 24 h at 4 °C, the cold insoluble precipitate, cryoprecipitate, is separated by centrifugation.

3.2.1.1. Factor VIII concentrates

Plasma-derived FVIII concentrate is manufactured from cryoprecipitate by a variety of fractionation techniques. These include three main groups: conventionally purified, ion exchange or heparin affinity purified, and monoclonal antibody purified; the products in the latter two groups are usually considered to be high-purity concentrates. Recombinant factor VIII concentrate is made in cell culture using recombinant technology.

3.2.2.1. Intermediate-purity concentrates. (prepared solely by conventional precipitation techniques)

3.2.2.2. Factor 8Y (BPL). This product is fractionated from cryoprecipitate. Contaminant fibrinogen and fibronectin are removed by precipitation with heparin. Factor VIII is

Table 1. Factor VIII concentrates available in the UK.

Product (Manufacturer)	Availability (list price*)	Purification Specific viral inactivation steps	Specific activity i.u. mg^{-1} protein in vial (prior to albumin stabilizer)
Plasma derived			
Alpha VIII (Alpha)	Product Licence (£0.39)	HAC S/D	13–20 (>100)
Alphanate (Alpha)	Product Licence (£0.39)	HAC S/D Dry heat 80 °C 72 h	13–20 (>100)
Liberate (SNBTS)	Product Licence	IEC S/D	50–150
Monoclate P (Centeon)	Product Licence (£0.44)	MAC Pasteurized 60 °C 10 h	5–10 (>3000)
Replenate (BPL)	Product Licence (£0.48)	MAC S/D	2.5–10 (1500–1800)
Haemate P (Centeon)	Product Licence (£0.63)	Conventional Pasteurized 60 °C 10 h	2–6
8Y (BPL)	Product Licence (£0.32)	Conventional Dry heat 80 °C 72 h	2.5–4.0
Recombinant			
Bioclate (Centeon)	Product Licence (£0.52)	MAC	2–10 (>4000)
Helixate (Centeon)	Product Licence (£0.52)	MAC	8–30 (>3500)
Kogenate (Bayer)	Product Licence (£0.52)	MAC	8–30 (>3500)
Recombinate (Baxter)	Product Licence (£0.52)	MAC	2–10 (>4000)
Refacto (Pharmacia and Upjohn)	CTX	MAC S/D	15000

Abbreviations: HAC, heparin affinity chromatography; S/D, solvent/deteregent; IEC, ion exchange chromatography; MAC, monoclonal antibody chromatography. *Manufacturer's list price per unit – for licensed products; prices may change and discounts may be negotiable. Currently VAT is payable on recombinant concentrates and those derived from nonhuman plasma.

precipitated with glycine/sodium chloride and lyophilized. Dry superheating is then applied at 80 °C for 72 h.

3.2.2.3. Haemate P (Centeon). The source cryoprecipitate undergoes adsorption with aluminium hydroxide followed by glycine sodium chloride precipitation. The resultant precipitate is pasteurized at 60 °C for 10 h in the presence of stabilizers prior to a second sodium chloride precipitation. Albumin is added before lyophilization.

3.2.3.1. Ion exchange or heparin affinity-purified concentrates

3.2.3.2. Alpha VIII (Alpha). The cryoprecipitate solution is subjected to PEG precipitation to purify the antihaemophilic fraction. Viral inactivation is by organic solvent (Tri(*n*-butyl) Phosphate; TNBP) and detergent (polysorbate-80). Affinity column chromatography is used to purify further the AHF. The FVIII is concentrated by ultrafiltration, further purified by glycine/sodium chloride precipitation and lyophilized.

3.2.3.3. Alphanate (Alpha). The manufacture is identical to Alpha VIII but with the incorporation of two specific viral inactivation steps: a solvent–detergent treatment prior to purification using affinity column chromatography and heat treatment at 80 °C for 72 h following lyophilization.

3.2.3.4. Liberate (SNBTS). Liberate is manufactured from cryoprecipitate, and after washing and resuspension the concentration of fibrinogen and fibronectin are reduced by precipitation. After adsorption with aluminium hydroxide to remove residual prothrombin complex, the FVIII undergoes solvent/detergent treatment and ion exchange chromatography.

Table 2. Factor IX concentrates available in the UK.

Product (Manufacturer)	Availability (list price)	Purification Specific viral inactivation steps	Specific activity i.u. mg^{-1} protein in vial	Notes
Plasma derived				
Alphanine (Alpha)	Product Licence (£0.39)	IEC S/D	>200	
Alphanine (SD/VF) (Alpha)	Named patient basis	IEC S/D Nanofiltration	>200	Product licence submitted
HIPFIX (SNBTS)	CTX	IEC HAC S/D Dry heat 80 °C 72 h	50–150	Licence application in preparation
Mononine (Centeon)	Product Licence (£0.63)	MAC Sodium thiocyanate Ultrafiltration	150–250	
Replenine (BPL)	Product Licence (£0.36)	Metal chelate S/D	100–160	
9A (BPL)	Product Licence (£0.33)	Conventional Dry heat 80 °C 72 h	2.5–3.5	Also contains II and X
Beriplex PN (Centeon)	Named patient basis	Pasteurized 60 °C 10 h Nanofiltration		Also contains II, VII and X Product licence to be submitted
DEFIX (SNBTS)	Product Licence (transition arrangements)	IEC Dry heat 80 °C 72 h	1.5–3.0	Also contains II and X
Prothromplex (Immuno)	Named patient basis	Conventional Vapour heating 60 °C 10 h and 80 °C 1 h	1.0–3.0	Also contains II and X
Prothomplex T (Immuno)	Named patient basis	Conventional Vapour heating 60 °C 10 h and 80 °C 1 h	1.3–1.8	Also contains II, VII and X
Recombinant				
Recombinant IX (Genetics Institute)	CTX	Chromatography Nanofiltration	250–270	

Abbreviations: HAC, heparin affinity chromatography; S/D, solvent/detergent; IEC, ion exchange chromatography; MAC, monoclonal antibody chromatography.

3.2.4.1. Monoclonal antibody purified concentrates

3.2.4.2. Monoclate-P (Centeon). The cryoprecipitate is dissolved in a water–alcohol mixture in order to precipitate fibrinogen and cold-insoluble globulins. The prothrombin complex factors are removed by adsorption with aluminium hydroxide. The cryosolution is then concentrated and dialysed to remove alcohol and stabilizers are added prior to pasteurization in solution at 60 °C for 10 h. The diluted pasteurized solution is passed through an immunoaffinity resin column with a solid-phase murine monoclonal antibody to vWF. The column is washed and the FVIII is separated from vWF by elution with calcium chloride. After concentration using ultrafiltration, further purification by sepharose chromatography, the final product is lyophilized.

3.2.4.3. Replenate (BPL). Resuspended cryoprecipitate is cooled and the resultant precipitate, mostly fibrinogen and fibronectin, is removed by centrifugation. Viral inactivation is by the addition of TNBP and triton X-100. Following column chromatography with sepharose bound antifactor VIIIC murine monoclonal antibody, the FVIII is eluted with ethylene glycol. The effluent is further purified by ion-exchange chromatography and lyophilized.

Table 3. Concentrates for treating von Willebrand disease.

Product (Manufacturer)	Availability (list price)	Purification Specific viral inactivation steps	Specific activity i.u. mg^{-1} protein in vial (prior to stabilizer)
Alpha VIII (Alpha)	Named patient basis* Product Licence for haemophilia A	HAC S/D	
Alphanate (Alpha)	Named patient basis* Product Licence for haemophilia A	HAC S/D Dry heat 80 °C 72 h	5–15 vWF (50–100)
Haemate P (Centeon)	Product Licence (£0.63)	Conventional Pasteurized 60 °C 10 h	7–10 vWF
vWF VHP (LFB)	Named patient basis	IEC S/D	150–200 vWF
8Y (BPL)	Product Licence (£0.32)	Conventional Dry heat 80 °C 72 h	6–10 vWF

Abbreviations; HAC, heparin affinity chromatography; S/D, solvent/detergent; IEC, ion exchange chromatography; MAC, monoclonal antibody chromatography. *Under evaluation for vWD.

Table 4. Concentrates specifically designed for factor VIII/IX inhibitor management (excluding standard factor VIII/IX concentrates – see Tables 1 and 2).

Product (Manufacturer)	Availability (list price)	Purification Specific viral inactivation steps	Specific activity i.u. mg^{-1} protein in vial
Plasma derived			
Autoplex (Baxter)	Named patient basis	Conventional 60 °C, 6 days	N/A
Hyate C Porcine VIII (Speywood)	Product Licence (£0.86)	Polyelectrolyte chromatography None	100
Feiba (Immuno)	Product Licence (£0.60)	Conventional Vapour heating 60 °C 10 h and 80 °C 1 h	N/A
Recombinant			
NovoSeven (Novo Nordisk) recombinant VIIa	Product Licence (£11.75 per ki.u)	IEC MAC	50 ki.u

Abbreviations: S/D, solvent detergent; IEC, ion exchange chromatography; MAC, monoclonal antibody chromatography.

3.2.5.1. Recombinant factor VIII concentrates

3.2.5.2. Kogenate (Bayer) and Helixate (Centeon). The gene for factor VIII has been inserted into an established cell line from baby hamster kidney (BHK). The secreted recombinant FVIII is processed by multiple purification steps, including two ion-exchange chromatography gel filtration/size exclusion chromatography and double immunoaffinity chromatography using a murine monoclonal antibody. The purified recombinant FVIII is then stabilized by the addition of pasteurized human albumin.

3.2.5.3. Recombinate (Baxter) and Bioclate (Centeon). The genes for FVIII and vWF have been inserted into Chinese hamster ovary (CHO) cells. The vWF acts as a stabiliz er for FVIII in cell culture. The recombinant FVIII produced is purified by single immunoaffinity chromatography using a murine monoclonal antibody. There are

Table 5. Concentrates other than for treating haemophilia A, B and vWD.

Product (Manufacturer)	Availability	Purification Specific viral inactivation steps	Specific activity i.u. mg^{-1} protein in vial (prior to stabilizer)
Plasma derived		Conventional	
Fibrinogen (Immuno)	Named patient basis	Vapour heating 60 °C, 10 h 80° C, 1 h	
Fibrinogen (SNBTS)	CTX	Conventional Dry heat S/D 80 °C, 72 h*	> 85% clottable protein
Haemocompletten P Fibrinogen (Centeon)	Named patient basis†	Conventional Pasteurized 60 °C, 10 h	
Factor VII (BPL)	Named patient basis	Conventional Dry heat 80 °C, 72 h	1.2—2.0
Factor XI (BPL)	Named patient basis	Conventional Dry heat 80 °C, 72 h	3.0–4.5
Factor XIII (BPL)	Named patient basis	Conventional Pasteurized 60 °C, 10 h and dry heat 80 °C, 72 h	0.7–1.0
Fibrogammin P Factor XIII (Centeon)	Named patient basis†	Conventional Pasteurized 60 °C 10 h	4–10

Abbreviations: S/D, solvent/detergent; IEC, ion exchange chromatography; MAC, monoclonal antibody chromatography. †Product licence being submitted.

Table 6. Fibrin preparations (topical application only).

Product (Manufacturer)	Availability	Purification Specific viral inactivation steps	Specific activity
Beriplast Combiset (Centeon) Factor XIII Fibrinogen Thrombin Aprotinin	Named patient basis*	Conventional Pasteurized 60 °C 10 h	
Fibrin Sealant Kit (SNBTS) Fibrinogen Thrombin	CTX	Dry heat 80 °C 72 h S/D	> 85% clottable protein
Tisseel Kit (Immuno) Fibrinogen Fibronectin Plasminogen Thrombin Aprotinin	Named patient basis	Vapour heating 60 °C 10 h and 80 °C 1 h	Not applicable

*Product licence being submitted.

two subsequent ion exchange chromatography steps to complete the purification process. The purified recombinant FVIII is then stabilized by the addition of pasteurized human albumin.

3.2.5.4. Refacto (Pharmacia and Upjohn). The r-VIII SQ gene, which encodes a single chain 170-kDa polypeptide, was derived from full-length cDNA by removing the major part of the region encoding the B-domain. The r-VIII SQ vector system was inserted into CHO cells and cultured in a serum-free medium. The purification process comprises five different chromatography steps including immunoaffinity with monoclonal antibodies directed to the heavy chain of FVIII and a chemical solvent/detergent virus inactivation step.

3.2.5.5. Animal protein and human albumin in recombinant FVIII. Kogenate and Helixate contain trace hamster protein, trace murine immunoglobulin and human albumin as a stabilizer but no vWF. Recombinate and Bioclate contain trace amounts of hamster, bovine and mouse protein, human albumin as stabilizer and a trace of human vWF. Refacto contains trace amounts of hamster protein and murine immunoglobulin and the final product is formulated without addition of human albumin.

3.3.1.1. Von Willebrand factor concentrates

The following concentrates contain vWF: *8Y, Haemate P and Facteur vWF concentrate. Alpha VIII* and *Alphanate* also contain vWF and are under clinical trial in vWD.

3.3.1.2. Facteur von Willebrand (Laboratoire Français de Fractionement et des Biotechnologies)

This vWF concentrate is prepared from solvent/detergent-treated cryoprecipitate by two DEAE chromatography steps to separate vWF from most cryoproteins, including FVIII. Further chromatography over immobilized gelatin results in removal of fibronectin.

3.4.1.1. Prothrombin complex concentrates (PCCs)

3.4.1.2. 9A (BPL). This concentrate, containing factors II, IX and X, is prepared from cryoprecipitate supernatant and is purified by DEAE ion exchange chromatography. After lyophilization it is heated at 80 °C for 72 h.

3.4.1.3. Beriplex PN (Centeon). This is prepared from cryoprecipitate supernatant by adsorption to aluminium hydroxide; the eluate containing factors II, VII, IX and X is pasteurized prior to nanofiltration as an additional virus inactivation step followed by lyophilization.

3.4.1.4. DEFIX (SNBTS). DEFIX, which contains factors II, IX and X, is prepared from cryoprecipitate supernatant by anion exchange chromatography using fractions whose low thrombogenicity potential have been selected by *in vitro* tests. After lyophilization it is heated at 80 °C for 72 h.

3.4.1.5. Prothromplex (Immuno). This is prepared from cryoprecipitate supernatant from which factors II, IX and X are adsorbed on to DEAE sephadex. The eluate is further processed and the product vapour heated as a specific viral inactivation step.

3.4.1.6. Prothromplex T (Immuno). This is prepared by mixing factor VII, prepared from DEAE sephadex adsorbed supernatant, with factors II, IX and X to produce Prothromplex T. Viral inactivation is by vapour heating.

3.5.1.1. Concentrates for treatment of inhibitor patients

3.5.1.2. Autoplex T (anti-inhibitor coagulant complex) (Baxter). Autoplex is made from cryoprecipitate supernatant which is subjected to a process of controlled activation. The lyophilized preparation is heat treated for 144 h at 60 °C.

3.5.1.3. FEIBA (factor eight inhibitor bypassing activity) (Immuno). This product is prepared from cryoprecipitate supernatant which then undergoes controlled generation of FEIBA. After a series of purifying adsorption and filtration steps the product is vapour heated for 10 h at 60 °C followed by 1 h at 80 °C and lyophilized.

3.5.1.4. Hyate C – porcine factor VIII (Speywood). Cryoprecipitate is prepared from porcine plasma and the factor VIII purified by affinity chromatography using polyelectrolyte resin. The final product is lyophilized. No additional stabilizing proteins are added.

3.5.1.5. NovoSeven – recombinant factor VIIa (Novo Nordisk). Factor VII is produced as a single-chain glycoprotein (406 amino acids, 50 kDa), in a genetically transformed BHK cell line. Purification is by ion-exchange and immunoaffinity chromatography using murine monoclonal antibodies. During purification recombinant FVII is converted to the two-chain activated form. The recombinant VIIa is formulated as a freeze-dried preparation. The recombinant VIIa contains non-coagulation factor contaminants as a result of the manufacturing process. These include trace amounts of hamster proteins from cells used in the fermentation process; bovine IgG and other bovine proteins from the bovine serum in the fermentation medium; and mouse

IgG from the anti- FVII monoclonal antibody used in purification.

3.6.1.1. Factor IX concentrates

3.6.1.2. Alphanine (Alpha). This concentrate is manufactured from cryoprecipitate supernatant by DEAE ion exchange chromatography. The viral inactivation process is by treatment with TNBP and detergent (polysorbate-80). After barium precipitation further purification of factor IX is achieved by dual polysaccharide affinity chromatography steps. The factor IX is formulated with heparin and dextrose and lyophilized.

3.6.1.3. Alphanine SD/VF (Alpha). This product is manufactured as for Alphanine but following affinity chromatography it is nanofiltered as an additional viral removal step.

3.6.1.4. HIPFIX (SNBTS). HIPFIX is manufactured by ion exchange chromatography from cryoprecipitate supernatant. After two ion exchange purification steps, it undergoes solvent/detergent treatment, heparin affinity chromatography, lyophilization and dry heat treatment at 80 °C for 72 h.

3.6.1.5. Mononine (Centeon). A PCC is made by standard methodology using ion exchange DEAE chromatography and applied to an immunoaffinity chromatography column containing a monoclonal antifactor IX antibody and the FIX is eluted using sodium thiocyanate which is removed by diafiltration. Dual ultrafiltration allows passage of FIX (but retention of viruses) which is then concentrated and added to aminohexyl-sepharose gel to remove trace residual murine antibodies. After elution from the gel, the FIX is lyophilized.

3.6.1.6. Replenine (BPL). Cryoprecipitate supernatant is adsorbed to an ion-exchange gel, washed with a low salt buffer, and FIX eluted with a buffer containing a higher concentration of sodium chloride. After viral inactivation by TNBP and Tween 80 the FIX is further purified by copper-sepharose chromatography which allows removal of other contaminating proteins. After formulation in lysine the product is lyophilized.

3.6.2.1. Recombinant factor IX concentrate

3.6.2.2. Recombinant factor IX (Genetics Institute). Recombinant human factor IX is expressed by CHO cells and purified using four sequential chromatographic steps and a final viral retention filtration step. The CHO cells are grown and produce recombinant FIX in defined, serum-free medium lacking any added protein components. Following purification, the recombinant FIX is diafiltered into an albumin-free formulation and lyophilized.

3.7.1.1. Coagulation factor concentrates for less common disorders

3.7.2.1. Fibrinogen concentrates

3.7.2.2. Fibrinogen (Immuno). Fibrinogen is prepared from cryoprecipitate supernatant after treatment with DEAE sephadex. Vapour heating is used to virally inactivate the product.

3.7.2.3. Fibrinogen concentrate (SNBTS). This is prepared from cryoprecipitate and after lyophilization it is dry heated at 80 °C for 72 h. A similar product with additional solvent/detergent treatment is under development.

3.7.2.4. Haemocomplettan P (Centeon). The fibrinogen is prepared from the glycine supernatant of the intermediate-purity FVIII process. The final product is a purified concentrate of fibrinogen pasteurized at 60 °C for 10 h.

3.7.3.1. Fibrin sealants

3.7.3.2. Beriplast P Combiset (Centeon). This fibrin sealant kit consists of a vial of human fibrinogen plus human FXIII connected to a diluent vial containing bovine aprotinin solution and a second vial of human thrombin connected to a diluent vial containing calcium chloride solution. The plasma components are pasteurized at 60 °C for 10 h. Aprotinin of bovine origin and calcium chloride solutions are also included.

3.7.3.3. Fibrin Sealant Kit (SNBTS). Fibrin Sealant is a multicomponent product comprising vials of human fibrinogen, human thrombin, calcium chloride and tris. The human fibrinogen is a freeze-dried preparation which also contains factor XIII and fibronectin. This component is manufactured from cryoprecipitate and is subjected to solvent/detergent treatment and a terminal, dry heat treatment at 80 °C for 72 h. Human thrombin is a freeze-dried preparation manufactured from cryoprecipitate supernatant plasma by ion exchange chromatography and is also subjected to solvent/detergent and dry heat treatment at 80 °C for 72 h.

3.7.3.4. Tisseel Kit (Immuno). Tisseel concentrate contains human fibrinogen, fibronectin, FXIII and plasminogen. Two concentrations of human thrombin are included in the kit to allow for either rapid (within 4 seconds) or

delayed (up to 60 seconds) setting of the sealant dependent on the type of operative procedure being performed. The kit contains bovine aprotinin. Both the Tisseel and human thrombin components are subjected to vapour heating.

3.7.4.1. Other concentrates

3.7.4.2. Factor VII (BPL). This is prepared from cryoprecipitate supernatant. The final product is lyophilized and heated at 80 °C for 72 h.

3.7.4.3. Factor XI (BPL). This is prepared from cryoprecipitate supernatant. Factor XI co-fractionates with ATIII on heparin– sepharose. The FXI-rich fraction is formulated, lyophilized and dry-heated at 80 °C for 72 h. Heparin has been added to reduce thrombogenicity.

3.7.4.4. Factor XIII (BPL). This is prepared from cryoprecipitate supernatant by precipitation with ethanol. Further precipitation steps purify the factor XIII which is then stabiliz ed with added albumin. Virus inactivation is achieved by pasteuriz ation (60 °C for 10 h) and dry heat (80 °C for 72 h).

3.7.4.5. Fibrogammin P (Centeon). This FXIII concentrate is prepared from cryosupernatant which is then further purified by ion-exchange chromatography prior to pasteuriz ation at 60 °C for 10 h. Albumin is added as a stabilizer.

4. Safety data on which recommendations are based

4.1.1.1. Transfusion transmitted viral infection

Several factors have contributed to the improved viral safety of modern plasma-derived coagulation factor concentrates. These include donor self-exclusion and screening policies, viral testing of plasma pools and specific virucidal procedures included in the majority of concentrate manufacturing processes. Currently individual human plasma donations are tested for anti-HIV 1 and 2, anti-HCV and HBsAg. Clinicians should consider checking with the manufacturer for information about further screening processes as additional tests may be introduced in future.

Reports of possible transmission of viral infection associated with the use of coagulation factor concentrates continue to be published. Such reports must be carefully scrutiniz ed since infection may be acquired by other routes. Data from carefully conducted, prospective previous untreated patient (PUP) studies provide substantial evidence of safety [6]. Systematic post-licensing pharmacosurveillance provides further evidence of viral safety.

4.1.1.2. HIV (1 & 2) infection. HIV transmission has not been reported by concentrates treated by dry heat treatment at 80 °C for 72 h, pasteurization at 60 °C for 10 h, solvent/detergent or vapour heating. Current methods are therefore effective in preventing HIV and, barring failure of manufacturing processes, the risk of infection is very small [7–13].

4.1.1.3. Hepatitis. The risk of hepatitis has been markedly reduced but not eliminated. Concentrates subjected to dry heating at 80 °C for 72 h appear to carry a very low risk of transmission of hepatitis [7, 8]. Solvent/detergent-treated factor concentrates also have an excellent safety record for hepatitis B and C in several PUP studies but their use continues to be linked with outbreaks of hepatitis A [11, 12, 14, 15]. PUP studies of viral safety of pasteurized products indicate a very low risk of hepatitis infection. At least seven cases of hepatitis B or C have been reported in patients who have received virally inactivated factor concentrates [9, 10, 16–19].

4.1.1.4. Parvovirus B19. Heat treatment, pasteurization and solvent/detergent methods of sterilization have been largely ineffective in preventing transmission of parvovirus B19 [20, 21]. It may sometimes cause hypoplastic anaemia and severe systemic illness even in those with apparent normal immunity. Maternal infection can lead to hydrops fetalis and miscarriage. The resistance of parvovirus to currently used virucidal processes raises concerns over the failure of these methods to inactivate other, as yet unidentified, agents [22, 23].

4.1.1.5. Cross-species infection. Theoretical concerns exist over the possibility of transmission of infection by viruses, or other agents, from mammalian cell cultures or other processes using animal proteins. There are, however, no data to support this.

Porcine FVIII produced from porcine plasma also carries the theoretical risk of infection. The pigs used in the manufacture of this product are screened for several known porcine viruses but the concentrate is not subjected to specific virucidal treatment.

4.1.1.6. Creutzfeld–Jakob disease (CJD). The theoretical possibility of CJD transmission by transfusion has been extensively examined. There is no evidence that the causative agent is transmitted by plasma products. There have been no links between CJD and haemophilia [24].

4.2.1.1. Immune function

Abnormalities of immune function in patients with haemophilia, occurring independently of HIV, have been

associated with the use of intermediate- and low-purity clotting factor concentrates [25]. These include decreased CD4 and increased CD8 cell numbers, decreased IL2 secretion, cutaneous anergy and various defects of monocyte function. The reported immune changes may be due to non-HIV viruses or chronic liver disease.

The CD4 count in HIV-infected patients has been shown to stabilize (or decline more slowly) in patients treated with high-purity or recombinant factor VIII concentrate whilst declining significantly in patients treated with intermediate-purity products [26–28]. No difference, however, in CD4 levels has been noted when patients on monoclonally or ion exchange prepared concentrates have been compared [29]. A survival advantage for the change to high-purity factor VIII concentrate has not been demonstrated [30, 31].

4.3.1.1. Inhibitors

Retrospective studies have shown a prevalence of factor VIII inhibitors of 6–20%. A higher incidence (25–28%) has been observed in recent prospective studies of inhibitor development amongst PUPs treated with high-purity or recombinant FVIII [32, 33]. Two prospective studies of inhibitor formation in patients treated with intermediate-purity factor VIII concentrate have shown a similar cumulative incidence of inhibitor formation to that observed with high-purity or recombinant FVIII concentrates [34, 35], suggesting that the use of high-purity, or recombinant FVIII concentrate does not confer an increased risk of inhibitor formation.

Neoantigens may form during viral inactivation processing causing inhibitors to arise in previously untreated patients [36, 37]. This problem was associated with concentrates no longer manufactured, but surveillance is advised following the change of product.

The diagnosis and management of inhibitors is beyond the scope of this report, and is the subject of separate UKHCDO recommendations [38].

4.4.1.1. Thrombosis, myocardial infarction and DIC

4.4.1.2. Prothrombin complex concentrates. Thromboembolism, disseminated intravascular coagulation and myocardial infarction have been associated with the use of prothrombin complex concentrates [39]. These complications are believed to be caused by activated coagulation factors. The risk is dose related, and may be increased by surgery or major bleeding. Thrombotic problems occur most commonly in patients with underlying cardiovascular disease and those who are immobile for long periods. Patients with pre-existing liver disease and premature infants seem particularly susceptible to develop DIC when treated with PCCs.

High-purity factor IX concentrates contain only trace amounts of other clotting factors. These products have no observable tendency to cause a clinically significant prothrombotic state and there is no evidence that activation of the coagulation system or thrombosis is associated with their use [40, 41].

4.4.1.3. Factor XI concentrate. Use of factor XI concentrates, particularly in high doses, has been associated with thrombosis [42]. Recent experiments have shown that doses 2–4 times greater than those recommended showed a thrombotic effect in the Wessler venous stasis model equivalent to that found with intermediate- purity factor IX concentrates. Elderly patients and those with a previous history of thrombosis or ischaemic heart disease are particularly at risk [43].

5. Licensing status

5.1.1.1. The regulations governing the prescription of medicines in the UK are likely to change and up-to-date information can be obtained from The Medicines Control Agency Information Centre (Tel: +44 (0) 171 2731678). Leaflets explaining different aspects of the regulations are available from the MCA Information Centre.

Drugs, including coagulation factor concentrates, are made available under the *Medicine Act 1968*; a summary of the different licensing arrangements is given in 'A Guide to the Provision of the Medicines Act affecting Doctors and Dentists' MAL 30, revised June 1985. The following is a brief synopsis of the legal arrangements under which drugs may currently be prescribed.

5.1.1.2. Product licence (PL). The PL indicates that the Licensing Authority has satisfied itself of the drug's safety, quality and efficacy and that the Committee on Safety of Medicines may have been consulted. The approved indications, doses and approved routes of administration are set out in the Data Sheet or Summary of Product Characteristics. The manufacturer bears liability for production of the drug.

5.1.1.3. Clinical Trial Certificate (CTC). As the *Medicines Act 1968* requires considerable documentation from the manufacturer before issuing a CTC this procedure has now been replaced by the CTX under the Medicines Exemption from Licences (Clinical Trials) Order, 1981 (SI 1981 no. 164)

5.1.1.4. Clinical Trial Exemption (CTX). The issue of a CTX indicates that the Licensing Authority has not objected to the trial which it does without reference to the Committee on Safety of Medicines. The trial is initiated by the manufacturer who bears liability for the product

and usually provides indemnity for patients under the 'good faith' interpretation of the ABPI Guidelines.

5.1.1.5. Doctors and Dentists Scheme (DDX). These provisions apply to the trial of an unlicensed drug by a doctor or dentist (not the drug company). The doctor or dentist bears liability for both the manufacture of the drug and the trial. Local ethical approval is required.

5.1.1.6. Named Patient Basis. When an unlicensed drug is prescribed by a doctor outwith a CTC or CTX, usually to treat an individual patient, this is on a 'named patient basis'. The doctor will bear liability for the prescription and clinical use of the drug. The manufacture may be covered by the *Consumer Protection Act, 1987.* It is recommended, however, that appropriate indemnity is obtained from the manufacturer, or its agent, prior to clinical use. Hospital Trusts are now drawing up rules for the use of unlicensed drugs, or licensed drugs for unlicensed purposes. Clinicians should therefore seek permission from the appropriate authority in the Trust to ensure their protection through Crown Indemnity. Before using a drug on a 'named patient basis' the practitioner must satisfy him/herself that its use is reasonable and in the interest of the patient. In the event of an adverse reaction he/she may be called upon to justify his/her actions. The doctor should explain to the patient that the drug is unlicensed and that its use is experimental; he/she should be advised that the extent and severity of contra-indications and side-effects may still not be fully appreciated. This basis for prescribing may be appropriate when there is no licensed suitable alternative.

When a drug with a PL is prescribed for a nonlicensed indication it is prudent to assume that it will be issued on a 'named patient basis' with the responsibility that this implies.

5.1.1.7. European Licensing system. This system is administered by the European Medicines Evaluation Agency and applies to all products of biotechnology. These products have a European Licence number and are marketed in the same packaging and with the same instruction leaflets in appropriate languages throughout the European Community.

6. Therapeutic guidelines

6.1.1.1. General recommendations

6.1.2.1. Patient information and consent

Good practice dictates that the necessity for treatment is appropriately explained to the patient and/or parent. This should include the advantages and risks of different therapies to allow an informed decision to be made. When consent has been obtained this should be recorded in the case notes.

6.1.3.1. Vaccination against hepatitis A and B

All patients who are not immune to hepatitis A or B and who currently receive, or may require, blood products should be vaccinated. At present revaccination with hepatitis A vaccine is not recommended and the vaccine is not currently licensed for use in children under the age of 1 year. Immunity to hepatitis B requires periodic reassessment and revaccination when appropriate. Carers who are preparing and/or injecting blood products should be protected by hepatitis A and B vaccine, if not immune.

6.1.4.1. Risk reduction

The use of fractionated, virucidally treated, concentrates when available has been the treatment of choice in achieving haemostasis in congenital coagulation factor deficiency since these products carry a lower risk of transmitting serious viral infection than cryoprecipitate or FFP [44] (*Grade B recommendation based on level III evidence*). Coagulation factor concentrates are also now available to treat patients with rare disorders. It is acknowledged that current viral inactivation techniques fail to eliminate virus transmission (see 4.1.1.1). This is particularly true for nonenveloped viruses which continue to be transmitted despite attempts to develop new virucidal techniques. Furthermore, some of these have led to additional serious complications in the patients, e.g. antifactor VIII antibody development following infusion of double virally inactivated concentrate. For these reasons recombinant factor VIII is now recommended treatment instead of plasma-derived concentrates. Frequent changing from one concentrate to another may encourage inhibitor formation and should therefore be avoided without good reason [36] (*Grade A recommendation based on level Ib evidence*). In addition the number of different batches to which a patient is exposed should be limited by use of a batch dedication system.

6.1.5.1. Use of DDAVP (desamino-8-D-arginine vasopressin, desmopressin)

DDAVP should be considered for all patients with mild/moderate haemophilia A or mild vWD, as this avoids the risk of viral transmission and is less expensive [45] (*Grade B recommendation based on level IIa evidence).*

DDAVP is generally administered intravenously at a dose of 0.3 μg kg^{-1} diluted in 50 mL of 0. 9% saline and infused over 20 min. An unlicensed intranasal spray

preparation of DDAVP (Octim Nasal Spray, Ferring) is available at a dose of 300 μg for adults and 150 μg for children. An unlicensed concentrated subcutaneous preparation (Octim injection, Ferring) is also available and should be given at the usual dose of 0. 3 μg kg^{-1}. Efficacy should be demonstrated irrespective of the route employed, by measuring FVIII/vWF. Intranasal DDAVP has been shown to be comparable to the effect of an intravenous dose of 0. 2 μg kg^{-1} DDAVP [46].

DDAVP should be used with caution in elderly individuals, pregnant women and avoided in those with evidence of arteriovascular disease. Precautions to prevent fluid overload leading to hyponatraemia must be taken particularly in young children and DDAVP is probably best avoided in those younger than 2 years of age.

6.1.6.1. Tranexamic acid

Tranexamic acid is an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin and is available in an intravenous or oral preparation (both in suspension and tablet form). It is particularly useful for bleeding from the gastrointestinal tract, menorrhagia, open wounds, dental surgery and in conjunction with DDAVP [47, 48] (*Grade A recommendation based on level Ia evidence*).

The recommended intravenous dose is 10 mg kg^{-1} 2–3 times daily and the oral dose 25 mg kg^{-1} 2–3 times daily [49] (*Grade B recommendation based on level IIa evidence*). Tranexamic acid is contra- indicated in patients with thromboembolic disease and should be avoided in patients with haematuria. It should not be used with FEIBA or other prothrombin complex concentrates (*Grade C recommendation based on level IV evidence*). Tranexamic acid can be used in combination with NovoSeven.

6.1.7.1. Fibrin sealant/topical thrombin

A number of topical agents are in use to promote local haemostasis. Fibrin sealant/glues have been used successfully in patients with acquired and congenital coagulation disorders [50] (*Grade B recommendation based on level III evidence*).

6.2.1.1. Specific recommendations

Licensed coagulation factor concentrates should be used in preference to unlicensed products. Unlicensed concentrates should be used, if possible, under formal clinical trial rather than on a 'named patient basis'. Each patient should be considered individually taking into account the following recommendations.

6.2.2.1. Haemophilia A – factor VIII deficiency

For patients for whom coagulation factor concentrate is the treatment of choice the following therapeutic strategies are recommended.

Recombinant factor VIII is the treatment of choice for all patients. If the introduction of recombinant factor VIII has to be prioritized then those who may benefit most should receive it first. Priority should therefore be given to those who have been least exposed to blood products in the past. These will most commonly be children. The following is therefore, in general, the order of priority for the introduction of recombinant factor VIII.

6.2.2.2. HIV antibody-negative patients.

(a) Previously untreated patients (usually small children): patients of any age not previously exposed to blood products should be treated with recombinant FVIII as this carries the lowest risk of viral transmission [32, 33] (*Grade B recommendation based on level IIb evidence*).

(b) HCV-negative patients: these patients will mostly be those who have been treated exclusively with virally inactivated concentrates. To minimize the chance of future exposure to viral infection these individuals should be treated with recombinant FVIII (*Grade B recommendation based on level IIb evidence*).

(c) HCV-positive patients: for these patients the case for the use of recombinant FVIII, rather than plasma-derived FVIII, is the prevention of infection with other blood borne viruses (*Grade B recommendation based on level IIb evidence*).

HIV antibody-positive patients. As there is evidence that the use of high-purity plasma-derived products and recombinant factor VIII are associated with better preservation of immune function it is recommended that these products continue to be used [26–28] (*Grade A recommendation based on level Ib evidence*).

6.2.3.1. von Willebrand disease. DDAVP should be used for DDAVP-responsive vWD patients in preference to plasma-derived products. Where DDAVP is not likely to be effective, or is contra- indicated, FVIII concentrate or purified von Willebrand factor is the treatment of choice [51] (Table 3). Cryoprecipitate is not virally inactivated, carries a risk of virus transmission and therefore should be avoided. It is, however, recognized that there may be some circumstances in which its use may be justified (*Grade B recommendation based on level IIb evidence*). Detailed guidance is given in the UKHCDO Guidelines on von Willebrand disease.

6.2.4.1. Haemophilia B – factor IX deficiency

Patients with factor IX deficiency should be treated with

high-purity FIX concentrates because they cause less haemostatic activation than PCCs [40, 41] (*Grade A recommendation based on level Ib evidence*).

6.2.5.1. Factor XI deficiency

The majority of patients with FXI:C levels < 15 u dL^{-1} will suffer excessive bleeding following trauma or surgery and should be managed with infusions of factor XI concentrate [42]. In those with partial deficiency of factor XI (15–70 u dL^{-1}) bleeding is more difficult to predict. Where there is a clear history of abnormal bleeding and haemostatic support is required, the use of FXI concentrate is justified. The dose of FXI should be sufficient to raise the level of factor XI: C to 70 u dL^{-1} and should not exceed 100 u dL^{-1} because of the risk of thrombosis (maximum dose 30 u kg^{-1}) [43, 52] (*Grade C recommendation based on level IV evidence*). Where there is no helpful history of bleeding, tranexamic acid may be used alone, but in the event of subsequent excessive bleeding must be replaced by FXI concentrate. Patients should be assessed for pre-existing risk of thrombosis and the concentrate should be used with great caution in those with a history of cardiovascular disease (*Grade C recommendation based on level IV evidence*). FFP might be a suitable alternative when FXI concentrate is contraindicated.

6.2.6.1. Factor VII deficiency

A purified, heat-treated FVII concentrate is available. This should replace PCCs and FFP as the treatment of choice in situations in which haemostatic support is necessary. The dose of FVII required depends on the severity of the deficiency and on clinical circumstances. The level of FVII required for haemostasis may be as low as 10–20 u dL^{-1} and this can be achieved by administering 5–10 i. u. FVII kg^{-1} (*Grade C recommendation based on level IV evidence*).

6.2.7.1. Factor II or X deficiency

There is currently no specific factor II or X concentrate available and PCCs (see section 3.4.1.1.) remain the treatment of choice (*Grade C recommendation based on level IV evidence*).

6.2.8.1. Factor V deficiency

There are no specific concentrates available for use in FV deficiency and therefore FFP is the only available treatment (*Grade C recommendation based on level IV evidence*).

6.2.9.1. Factor XIII deficiency

FXIII concentrate prepared from human plasma is now available and is the treatment of choice (*Grade C recommendation based on level IV evidence*).

6.2.10.1. Fibrinogen deficiency

Unlicensed concentrates of fibrinogen have recently become available and since these products are virally inactivated it is anticipated that they may replace cryoprecipitate in the near future (*Grade C recommendation based on level IV evidence*).

6.2.11.1. Coagulation factor concentrates for treating patients with inhibitors

The products available for the treatment of patients with coagulation factor inhibitors are given in Table 4. Their use is considered in the *UKHCDO Guidelines* [38].

6.2.12.1. Future treatment of hereditary coagulation disorders

Recombinant factor VIII is likely to be used widely because of the continuing difficulty in the production of safe plasma-derived concentrates. It is anticipated that recombinant factor VIII, which is formulated without addition of human albumin as a stabilizer, will become licensed. Furthermore it is hoped that recombinant factor VIII will eventually be manufactured without using any bovine or human proteins.

Recombinant factor IX may become licensed when it should be introduced to routine haemophilia care using similar criteria as for recombinant factor VIII.

7. Clinical audit

The regular assessment of therapeutic practice by audit is an essential component of good haemophilia practice. Adherence to these guidelines may be audited in many ways, for example:

1 Are patients receiving the appropriate recommended product?

2 Are there appropriate pharmacosurveillance arrangements in place, e.g. viral infection and inhibitor formation?

3 Are there clear local arrangements to ensure that patients receive the appropriate treatment.

4 When a nonlicensed product is used are data collected which can be used to help with its evaluation?

5 Is there a system for recording adverse reactions and are these appropriately reported nationally?

8. Review of guidelines

An advance draft copy of these guidelines was reviewed by the following: Royal College of Physicians, Royal College of Pathologists, British Society for Haematology.

9. Declaration by Task Force members

Each member of the Task Force has received consultancy fees from between one and five product manufacturers. In some cases these have been paid into departmental funds or to UKHCDO.

Research funding for clinical trials or other research projects has been received from a total of 16 different pharmaceutical firms.

B. T. Colvin
Former Chairman
UK Haemophilia Centre Directors' Organisation
3 October 1996

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10. Appendix 1

Clinical guidelines recently produced by UKHCDO

Hay CRM, Colvin BT, Ludlam CA, Hill FGH, Preston FE. Recommendations for the treatment of factor VIII inhibitors: from the UK Haemophilia Directors Organisation Inhibitor Working Party . *Blood Coagulation and Fibrinolysis* 1996; **7** : 134 – 8.

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* *Guidelines for the Diagnosis and Management of von Willebrand Disease:Prepared by the von Willebrand Working Party of the United Kingdom Haemophilia Centre Directors' Organisation.*
* *Guidelines for the Use of Factor XI Concentrate .*
* *Prophylaxis in the treatment of haemophilic boys.*
* Copies obtainable from Miss R. J. D. Spooner, Oxford Haemophilia Centre, Churchill Hospital, Headington, Oxford OX3 7LJ, UK.

Appendix 2

Levels of evidence

Level	Type of evidence (based on AHCPR 1992)[5]
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of recommendations

Grade	Recommendation (based on AHCPR)
A (evidence levels Ia, Ib)	Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality