NOT FOR PUBLICATION

COMMERCIAL - IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Product Licence Number	PL/0116/0011
Report by	Dr Thomas
Meeting (a) (b)	December 1972 January 1973
Therapeutic Class	Blood product

(A) SUB-COMMITTEE ON TOXICITY AND CLINICAL TRIALS
(B) SUB-COMMITTEE ON BIOLOGICALS

MEDICINES ACT 1968 - APPLICATION FOR A PRODUCT LICENCE

Summary and Report

1. PRODUCT SUMMARY

1.1 Name of Product — HEMOFIL [Antihaemophilic Factor (Human) Method Four]

1.2 Licence to be held by — Travenol Laboratories Limited
Caxton Way, Thetford, Norfolk.

1.3 Manufacturer — Hyland Laboratories (Division of Travenol Laboratories)
Costa Mesa, California, USA.

1.4 Description — A sterile, lyophilised preparation of purified human Factor VIII (antihaemophilic factor)

1.5 Period of Validity — 5 years

1.6 Proposed Method of Sale — Prescription only

1.7 Consideration of this application by other Sub-Committees

a) Sub-Committee on Chemistry Pharmacy and Standards - not referred
b) Sub-Committee on Biological Standards - January 1973
c) Sub-Committee on Toxicity, Clinical Trials and Therapeutic Efficacy - December 1972

2. PHARMACEUTICAL FORM

The product is a sterile, lyophilised preparation of purified anti-haemophilic factor (Human) in a single dose glass container, packaged with a suitable volume of water for injection USP for reconstitution into a form for intravenous administration. Anti-haemophilic factor (Human) is identical to Blood Coagulation Factor VIII.

3. CLINICAL USE

3.1 Recommended clinical use

The product is intended for use in the therapy of classical haemophilia (Haemophilia A) and correction of partial AHF difficiencies. It has also proved valuable in patients with acquired Factor VIII inhibitors.

3.2 Route of administration

After reconstitution the product is administered intravenously.

3.3 Recommended dosage

Each bottle of anti-haemophilic factor (HEMOFIL) is labelled with the number of AHF units which it contains, one AHF unit being defined as the activity present in 1 ml of average normal pooled human plasma less than one hour old (100% AHF level). The amount of AHF which a haemophiliac requires for normal haemostasis varies with circumstances and with the patient. The amount to be supplied depends on the degree of deficiency and on the AHF level desired. The following formulae can be used to calculate approximately the expected response from a given dose, or the dose required for a given effect:

(i) Units required = body weight (kg) x 0.4 $\times$ desired AHF increase (in % of "normal") or

(ii) Expected AHF increase (in % of "normal") = $\frac{\text{units administered}}{\text{body weight (kg)} \times 0.4}$

There is some evidence that in a haemophiliac with severe bleeding, particularly if he has not been recently treated, up to double the calculated initial dose may be needed to produce the desired AHF level, after which the formulae apply.

The half life of AHF administered to haemophiliacs has been variously estimated at 8-24 hours. Although dosage can be estimated by these calculations, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patients' plasma at suitable intervals to ensure that adequate AHF levels have been reached and are maintained. If the AHF level fails to reach expected levels, or the bleeding is not controlled after apparently adequate dosage, the presence of AHF inhibitors should be suspected. By appropriate laboratory procedures, the presence of AHF inhibitors can be demonstrated and quantitated in terms of AHF units neutralised by each ml of plasma or by the total estimated plasma volume.

4. STANDARD PROVISIONS

All standard provisions shall apply to the licence.

5. MANUFACTURE AND ASSEMBLY

5.1 Antihaemophilic Factor (Human) Method Four is prepared by fractionation of fresh human plasma, from selected donors (see 11).

5.2 Place of Manufacture or Assembly

The AHF concentrate is manufactured at

Hyland Laboratories
Division of Travenol Laboratories International
PO Box 2214
3300 Hyland Avenue
Costa Mesa, California, 92626
USA

5.3 Sterile Water for Injection USP

This component is manufactured by

Travenol Laboratories Inc
6301 Lincoln Avenue
Morton Grove, Illinois, 60053
USA

5.4 Storage of the packaged product will be at the place of manufacture and assembly listed above.

After shipment to the United Kingdom, the product will be stored at the address of the proposed licensee:-

Travenol Laboratories Limited
Caxton Way, Thetford, Norfolk, England.

or at

Travenol Laboratories Limited
Bowles House
Poyle Estate
Blackthorn Road
Colnbrook
Buckinghamshire

6. QUALITY CONTROL

6.1 During the manufacture of the product Quality Control precautions ensure that the identity, strength, quality and purity conform to the product specification.

6.2 The proposed licensee will be responsible for deciding if any lot of the product is of acceptable quality for marketing.

7. CONTAINERS

Antihaemophilic Factor (Human) and Sterile Water for Injection USP are contained in glass vials. The vials are in turn packaged in a plastic unit which also includes the necessary needles, syringe or administration set presented sterile and non pyrogenic for single use.

The units should be stored between 2° and 8°C. Freezing, which might crack the diluent bottle, must be avoided.

8. LABELLING

A copy of the package leaflet which states particulars of directions for use, contraindications and warnings is attached to the submission (Appendix 5, part 2).

9. RECOMMENDED CLINICAL USE

This concentrate is not known to contain clotting factors other than AHF in sufficient quantity to be useful therapeutically. The concentrate can be of significant value in patients (not true haemophiliacs) with acquired Factor VIII inhibitors. In such other uses, the dosage of the concentrate should be controlled by frequent laboratory determinations of circulating AHF. With constant monitoring of the patient's physical condition, the product can be administered as rapidly as possible. If the AHF inhibitor level is low (5,000 units or less in the total plasma volume), direct intravenous syringe injection may be used. With high inhibitor levels (over 5,000 units), a rapid intravenous drip infusion is preferable.

All bottles of Hemofil contain the following warning on the label:

"The risk of transmitting hepatitis is present. No warranties are made or created. Warranties of fitness or merchantability are excluded."

10. CHEMISTRY AND PHARMACY

10.1 Name: Antihaemophilic factor (Human-Method Four) HEMOFIL

(Sterile Water for Injection USP is contained in a separate glass vial for reconstitution)

10.2 Description

Hemofil is a stable, lyophilised preparation of purified human anti-haemophilic factor (AHF) identical to blood coagulation Factor VIII in a nomenclature recommended by the International Committee for Nomenclature of Coagulation Factors (1954).

10.3 Method of Manufacture

The antihaemophilic factor concentrate is prepared by large scale fractionation of fresh human plasma. Human plasma cryoprecipitate is pooled and dissolved in sodium chloride solution containing glycine as

a stabiliser, sodium citrate and heparin as anticoagulants. After adjusting the pH, inactive proteins are precipitated by the addition of polyethylene glycol. After centrifugation, the AHF-rich portion is precipitated out of the supernatant by increasing the polyethylene glycol concentration. The precipitate is collected by centrifugation and is dissolved as described above for the cryoprecipitate. The AHF is precipitated at controlled pH, temperature and glycine concentration, leaving inactive proteins, and polyethylene glycol. The precipitate is dissolved in citrated saline (0.02 M trisodium citrate in 0.12 M sodium chloride) to a volume which will bring the AHF activity per ml. within the range required by the product specification. The resulting solution is clarified by centrifugation and/or filtration. It is sterilised by filtration and filled, under aseptic conditions, into sterile vials. The product is then frozen and lyophilised. When dry the vials are capped, under nitrogen pressure for the 10 ml. vial size, and a vacuum for the 30 ml size.

The vials are then labelled with the appropriate label and packed into 'kits'.

10.4 Reagents used

All conform to the specifications of USP XVIII

Non pyrogenic water

Sodium Chloride: Reagent grade; non pyrogenic.

Trisodium Citrate: Reagent grade, non pyrogenic.

Glycine: Reagent grade, non pyrogenic.

Sodium Heparin: 5,000/units/ml., non pyrogenic.

Polyethylene Glycol 4000: non pyrogenic.

Acetic Acid: Reagent grade.

Sodium Hydroxide: Reagent grade.

10.5 Quality Control Checks made at each stage of the process.

Human plasma is collected by plasmapheresis from blood banks under strict control of the manufacturer. All these blood banks must operate under the standards described by the Public Health Service Regulations for the Manufacture of Biological Products, title 42, Part 73 of the United States Department of Health, Education and Welfare.

11. ADMINISTRATIVE PROCEDURES

Blood donors that are used for plasmapheresis must be aged between 21 and 65 years of age. Donors between the ages of 18 and 21 may be used if this is allowed by state law and they have completed a consent and release form, signed by their parents. Their temperature must be normal and the systolic blood pressure shall be not over 180 nor under 110. The diastolic pressure shall not be over 100 nor under 60. The pulse rate must be between 60 and 110 per minute. The blood total protein must be in the range of 6-9 grams, and the albumin-globulin ratios must fall within the range 1.1-2.0. All donors are screened for Hepatitis Associated Antigen, using Hyland's HAA screening test (counter electropheresis).

Diluting Fluid (berbital-buffered saline)
0.03 M Calcium Chloride

b. Procedure

Dilutions 1:5, 1:10, 1:20 and 1:40 of the Reference Plasma and of the AHF test sample are prepared in Diluting Fluid. (The AHF test sample requires an initial dilution, dependent upon its potency of approximately 1:30 in Factor VIII Deficient Substrate). To tubes in a 37°C water bath, 0.1 ml each of Partial Thromboplastin, of Factor VIII Deficient Substrate and of a Reference Plasma dilution are added and incubated for exactly three minutes. Immediately 0.1 ml of pre-warmed 0.03 M calcium chloride is added, and the time in seconds required from this addition until the gel formation is observed while slowly and gently tilting the tube. The gel formation time for each AHF test dilution is determined.

c. Calculations

The clotting time in seconds for each Reference Plasma dilution is plotted against the % Reference Plasma concentration on semi-log graph paper. By interpolation the concentration of the Reference Plasma that would give the same clotting time as each AHF test sample dilution is determined.

The resulting equivalent Reference Plasma concentration multiplied by the dilution factor represents the AHF activity of the test sample plasma (ie, per cent of normal).

d. Limits

The limit is as labelled, with a minimum of 10 AHF units/ml.

14.3 The concentration of total protein and AHF units is determined during the processing as required to control the concentrations in the final product. In addition to these controls and those described under impurities, acute toxicity tests are employed. The test methods used and the limits for acceptance are in conformity with those outlined in US Department of Health, Education and Welfare, Public Health Service, Regulations Biological Products, Title 42 Part 73.

(Long term toxicity studies on this product are not possible on non-human species because of the human "species specific" antigenicity.)

15. QUALITY CONTROL

15.1 Units of Activity

Each vial of the AHF concentrate is labelled with the number of units of activity it contains. A unit of activity is defined as the quantity of Factor VIII normally present in one ml. of average normal pooled human plasma less than one hour old (100% AHF level).

Factor VIII is labile. During purification and concentration process, variable proportions of the activity normally present in the fresh plasma will be lost. There will, therefore, be a lot to lot variation in the potency of the final product.

15.2 Other constituents

Not applicable

15.3 Finished Product Specification (HEMOFIL)

a. Units of activity for the lyophilised AHF concentrate are as detailed for the individual constituents. The limit is as labelled with a minimum of ten (10) AHF units per ml. of reconstituted material

b. Total Protein Content in reconstituted material is a maximum of 4.0 mg. per AHF unit

c. Moisture content is a maximum of 2.0% of lyophilised product weight

d. Solubility when the contents of the final container are reconstituted at 37°C with the volume of Sterile Water for Injection USP designated, the material should be completely dissolved within 20 minutes.

e. pH The pH limits are 6.6 to 7.0 for reconstituted material

f. Glycine Content The limit is a 0.25 M maximum of reconstituted material

g. Polyethylene glycol content The limit is a maximum of 0.15 g. per 100 ml. of reconstituted material

h. Isoagglutinins Each lot of AHF concentrate is tested for its content in isoagglutinins. Whenever the titre of immune Anti-A or Anti-B isoagglutinins without neutralisation with blood specific substances is in excess of 1:640, the product will be labelled "group O specific" and will be recommended for use with group O recipients only.

i. Hepatitis The concentrate is prepared from large pools of fresh human plasma. Such plasma may contain the causative agents of viral hepatitis. However, each unit of plasma has been found to be negative for Hepatitis Associated Antigen by counterelectrophoresis.

j. Haemolysins There shall be no indication of the presence of haemolysins.

k. Sterility The product shall be sterile and non-pyrogenic after testing in accordance with Bureau of Biologics procedures.

l) Toxicity The product contains a trace amount of heparin 0.5 units (0.005 mg.) or less per ml of reconstituted material. It is not possible to test for the presence of heparin in trace amounts in Anti-haemophilic Factor. Consequently a series of experiments have been performed to demonstrate that concentrations of heparin many times greater than that which could result from the manufacturing process have no demonstrable effect after injection of the volumes encountered in the use of the product.

Data showing Heparin effect

Four component Partial Thromboplastin Times (PTT) 0.1 ml Partial Thromboplastin - Kaolin, 0.1 ml VIII Deficient Substrate, 0.1 ml HEMOFIL or dilution, 0.1 ml Calcium Chloride.

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Heparin added in varying concentrations to final product

Concentration of heparin in reference experiment (using HEMOFIL lot 591M013A)

	0.1 u/ml	0.25 u/ml	0.5 u/ml	0.75 u/ml	1.0 u/ml	no heparin
PTT	30.4 sec	33.7 sec	38.2 sec	45.1 sec	53.8 sec	29.8 sec

3 x 300 litre experimental lots of HEMOFIL to which 1 unit per ml of heparin was added "in process"

	964R041A	964R042A	964R043A
PTT	38.7 sec	31.2 sec	35.8 sec

16. DEVELOPMENT PHARMACEUTICS

The proposed formulation of the product offers the following advantages:-

a. It is of homologous origin.

b. It supplies 6 or more times higher potency AHF than the present glycine or cryoprecipitate preparations with relatively smaller amounts of fibrinogen and other protein, furnishing adequate AHF without excessively overloading the circulatory system.

c. Each lot is assayed and labelled for its AHF content, making possible estimation of dose needed and prediction of effect expected. (Dosage with plasma is less exact, since the AHF level in the plasma of normal individuals varies from about 50% to about 200% of normal).

d. Because of predictable effect, therapy may be managed without repeated determination of AHF level when the patient is very young, when veins are poor, or when laboratory service is not immediately available.

e. Blood group isoagglutinins are not present in clinically significant amounts. Therefore, the product may be safely used without time-consuming grouping, typing or cross-matching; however, these procedures should be done when possible.

f. In dry form, AHF appears very stable, in contrast to its erratic decay in fresh or frozen plasma.

g. This AHF preparation can be given rapidly, either by intravenous drip infusion or direct syringe injection, with no significant reactions.

h. In the experience thus far, urticaria has not been seen, and in haemophiliacs known to be allergic to plasma, no "plasma reactions" have been encountered,

i. Sufficient amounts may be administered to overcome inhibitors, thus eliminating the need for bovine or porcine preparations.

j. It reconstitutes rapidly and easily without formation of bubbles or foam which can inactivate AHF.

17. BIOLOGICAL AVAILABILITY

Since Antihaemophilic Factor (Human) is administered intravenously and is replacement therapy in patients with abnormally low levels of AHF, no studies of absorption or elimination can be done.

The half-life of AHF administered to haemophiliacs has been variously estimated at 8 to 24 hours. In the severe haemophiliac, the half-life of the first dose of AHF in any form appears to be at the lower end of the range, but for subsequent doses it may be safely estimated as at least 12 to 15 hours in the absence of inhibitors and "active bleeding".

18. METABOLIC STUDIES

Not applicable

19. STABILITY REPORTS

Antihaemophilic Factor (AHF) potency test results on the product initially and after storage for 24 months to 36 months in standard glass vials are listed on p.11.

20. PROPOSED SHELF LIFE FOR PRODUCT

1 year

21. CONTAINERS

The AHF concentrate is available in vial sizes of 10 ml and 30 ml, with minimum activities ranging from 100 - 550 units.

22. STABILITY DATA

See p.11.

23. DRAFT PACKAGE INSERT

A sample of the package leaflet is given as Appendix 5 (p.12 of Part 2 of the Submission)

24. REPORTS OF CLINICAL TRIALS

The only experience with Hemofil in the United Kingdom has been on an individual basis. Two patients have been treated at St Thomas' Hospital, apparently with successful results. Detailed descriptions of these two cases appear in a table immediately following page 6 in Part 5 of the Submission.

Since 1968, when the product became available in the United States, there has been a considerable experience of its use in the treatment of haemophilia.

HYLAND
ANTIHEMOPHILIC FACTOR (HUMAN)

Stability Data

LOT Number	Original Manufacturing Date	Original Potency units/vial	Original Moisture %	Date of Potency Retest	Potency Retest units/vial	Moisture Retest%	Solution Time Minutes	Spontaneous Clotting Time Days
0591H053A1	30 April 69	302	0.4	24 April 72	240		12	
0591H066A1	19 Aug 69	186	0.3	25 April 72	196	2.2	6	8
0591H077A1	20 Aug 69	184	0.6	19 April 72	158	2.2	18	14
0591H097A1	5 Aug 69	223	0.3	18 April 72	196	2.0	8	
0591H098A1	12 Aug 69	188	0.4	27 April 72	196	2.4	16	6
0591H099A1	19 Aug 69	181	0.4	27 April 72	189	1.8	17	6
0591H100A1	21 Aug 69	168	0.3	24 April 72	168	2.2	5	8
0591H102A2	28 Aug 69	189	0.8	5 April 72	168	2.0	9	23
0591H103A2	12 Sept 69	158	0.8	5 April 72	168	1.6	13	23
0591H105A1	15 Sept 69	183	0.5	23 Feb 72	196		4,5	5
0591H109A1	17 Sept 69	234	0.4	18 April 72	221	1.8	4	10
0591H112A1	26 Sept 69	244	0.6	3 March 72	214		6,6	3
0591H113A2	5 Oct 69	182	0.5	5 April 72	182	1.8	10	27
0591H117A1	18 Oct 69	154	0.3	23 Feb 72	197		7,8	5
0591H118A1	29 Oct 69	213	0.3	6 March 72	203		4,5	>3
0591H119A1	29 Oct 69	213	0.3	5 April 72	203	1.7	3	>27
0591H125A1	1 Dec 69	144	0.5	24 Feb 72	147		3.3	1
0591H129A1	19 Nov 69	145	0.6	29 Feb 72	126		3,4	6
0591H139A1	12 Jan 70	232	0.1	29 Feb 72	182		4,4	>9
0591H141A1	13 Jan 70	322	0.2	25 April 72	350	1.9	5	7

Results of the early American trials show that after infusion of Factor VIII in concentrated form, cessation of haemorrhage is prompt and post transfusion circulating levels of Factor VIII approach normal values. No allergic reactions were observed and fibrinogenaemia or hypervolaemia were not a problem. On the basis of the American experience, Travenol Laboratories make the following claims for their product:-

a. A higher potency of Factor VIII is contained in small volumes.

b. Exact standardisation of AHF activity makes possible calculations of dosage necessary to produce the desired increase in circulating AHF levels.

c. Sufficient amounts of the concentrate may be administered to patients with inhibitors to the AHF, thus eliminating the need for bovine or porcine preparations.

d. The AHF preparation can be given rapidly, either by intravenous drip infusion or direct syringe injection, thus reducing patient hospitalisation.

e. The concentrate may be used to treat haemophilia prophylactically, thus preventing minor bleeding episodes by maintaining normal haemostasis.

25. PUBLISHED PAPERS

25.1 Modern Treatment of Haemophilia with a potent, new AHF concentrate

E Shanbrom et al. Bibl haemat;l No 38 Part 1 pp 854-860 (Karger, Basel 1971)

A new, high-potency AHF concentrate has been produced within the past year and is now available for use in the treatment of haemophilia. Prepared from a pool of fresh human plasma, this glycine and polyethylene glycol-precipitated material contains from 30 to 100 units of AHF activity per ml. The total protein content is reduced to 1.9 mg/ml, thus indicating a purification factor of some 100 to 400 times that of plasma.

Fifty-four classical haemophiliacs have been successfully treated with this new concentrate. In all cases, clinical bleeding was stopped within minutes of infusion and the desired level of AHF achieved. In most cases, haemostasis was maintained for up to 7 days following single-dose therapy. No allergic reactions were seen, in spite of previous history of sensitisation in many cases. Fibrinogenemia was not a problem, nor was hypervolemia. In several cases, the concentrate was successfully administered by intravenous syringe injection making possible office or out-patient treatment. In addition, 17 patients with Factor VIII inhibitors were also administered this high-potency AHF concentrate. Initial doses of concentrate neutralized the amount of circulating inhibitor, and subsequent increased doses produced demonstrable AHF levels.

The advantages of haemophilia therapy using this new AHF concentrate are (i) higher potency of Factor VIII contained in smaller volumes (ii) exact standardization of AHF activity makes possible calculation of dosage necessary to produce desired increase in AHF level (iii) can be used to treat patients with inhibitors to AHF (iv) syringe injection makes possible office treatment and reduces patient hospitalization and (v) may be used to prophylactically treat haemophilia A, thus preventing minor bleeding episodes by maintaining normal haemostasis.

25.2 Rapid Correction of AHF Deficiency by Antihaemophilic Factor-Method Four, with Special Reference to Inhibitors

E Shanbrom Bibl haemat No 34 pp 52-59 (Karger, Basel/New York 1970)

Ideally an AHF fraction should have high activity, be inert antigenically, have effective duration in vivo, be stable for long periods, have no risk of hepatitis, not induce anticoagulants, be low cost and readily available, and be effective intramuscularly. While Method IV fulfills most of these criteria, unfortunately, it is not free of the risk of hepatitis and must be administered intravenously. It does have the added value of permitting successful out-patient or office management of haemophilia and the predictable treatment of Factor VIII inhibitors. Our work with even more highly fibrinogen-free fractions may overcome these remaining problems and perhaps even permit true maintenance or replacement therapy.

25.3 Continuous Intravenous Infusion of Factor VIII in Classic Haemophilia

C W McMillan et al. Brit J. Haemat 1971 18 659

The effects of continous intravenous infusion of Factor VIII were studied under varied conditions in five children with classic haemophilia; Factor VIII activity was stable at room temperature (73-76°F) up to 12 hours in cryoprecipitate from fresh plasma and up to 27 hours in glycine-precipitated fractions (Fraction AA and Method Four, Hyland). Constant infusion (17 ml/hr) of different concentrations of these fractions produced levels of plasma Factor VIII activity which were proportional to the dose-rate and became relatively steady after 12-18 hours. In separate studies of two of the subjects, dental extraction and laminectomies were uneventfully supported by an initial dose of Factor VIII followed by continuous infusions. It is suggested that continuous intravenous infusion of Factor VIII is useful for studying the regulation of Factor VIII levels in plasma and for maintaining steady plasma Factor VIII activity during replacement therapy.

25.4 Experimental Prophylaxis of Severe Haemophilia With a Factor VIII Concentrate E Shanbrom and G M Thelin JAMA 203, 1053, 1969.

A patient with severe haemophilia A was given long-term prophylactic treatment with an aminoacetic acid-precipitated preparation of human Factor VIII (antihaemophilic factor (AHF)). Dosage was based on units of AHF per kilogram of body weight required to maintain AHF levels between 80% and 100% of normal. Weekly intravenous infusions produced predictable AHF levels. Response to the concentrate was prompt. Haemostasis was achieved following two episodes of severe, spontaneous, intracerebral and gastrointestinal haemorrhage. Despite extensive bruising of the patient's entire body after an automobile accident, no haematomas developed. The preparation was well tolerated with no change in pulse rate or blood pressure. Neither hyperfibrinogenemia nor hypervolemia occurred. With the evidence provided by this case, and the availability of AHF concentrates for simple office or out-patient treatment, prophylaxis of severe haemophilia now appears feasible.

25.5 Administration of Single Doses of AHF (Factor VIII) Concentrates in the Treatment of Haemophilic Haemarthroses G R Honig et al. Pediatrics 43 26, 1969.

In the treatment of acute haemarthroses in AHF (Factor VIII) deficient patients it has been our practice to administer repeated infusions of plasma in order to maintain haemostatic levels of AHF over a 48 hour period. In the present study, AHF concentrates were administered so as to provide the entire therapeutic AHF replacement in a single infusion. Fifty-one episodes of acute haemarthrosis in 14 boys with AHF deficiency were treated with plasma cryoprecipitate, glycine-precipitated Factor VIII (Hyland), or a new higher potency AHF concentrate (Hyland Method Four). Single doses of 20 to 30 units of AHF activity per kilogram were given; this was sufficient to produce a post-infusion AHF level of 40 to 50%. In 47 of the 51 episodes treated, satisfactory resolution of the haemarthroses occurred without need for further AHF therapy. These results appeared at least as satisfactory as those using repeated plasma infusions. Advantages of therapy using single-dose infusions of AHF concentrates include fewer venipunctures, ease of administration, less need for hospitalization, and greater patient acceptance. Studies of Hyland Method Four AHF concentrate indicated that the dose-response relationship and survival of AHF activity in vivo are similar to that seen with other therapeutic forms of AHF.

26. MEDICAL COMMENT

The availability of Factor VIII concentrates represents a major advance in the care of patients with classical haemophilia. Such concentrates have enabled corrective orthopaedic procedures to be carried out, and for the first time there is a prospect of domiciliary treatment. The major disadvantage of currently available commercial preparations, such as HEMOFIL, is that they are prepared from very large plasma pools, and carry the risk of transmitting hepatitis virus. Hyland screen all their donors for hepatitis-associated antigen, which reduces but does not eliminate this risk. However, no attempt is made to disguise the risk of hepatitis, and it may be considered that the decision to use this material could be left to the individual clinician who can balance the potential hazard against the anticipated therapeutic benefit to the patient.

It is recommended that a product licence be granted.

DPT

SUMMARY OF INSPECTION REPORT

Hyland Laboratories, Costa Mesa, California, were inspected on October 24th, 1972. In addition, a commercial blood bank in downtown Los Angeles, owned and operated by Hyland, was also inspected.

The blood bank performed plasmapheresis on between 200-300 people daily. 1000 ml. blood was collected from the donors (in two steps) and the cells returned. This was done twice weekly on the "regular customers", who constituted about 50% of the total number of donors. The donors were all men, mostly middle-aged, and predominantly of Mexican origin. They were euphemistically described to me as "people who need $5", which is the amount they were paid for each donation of blood. From what I saw, they were certainly not affluent, although they could not fairly be described as down-and-out alcoholics. Neither did they seem to be youthful hippies, for the most part. However, the medical screening of the donors was rudimentary: a microhaematocrit determination of ear lobe capillary blood, blood pressure and temperature, and that was about all. Probably the most important screening carried out was routine testing for hepatitis-associated antigen, using Hyland's own counterelectrophoresis kit. This testing is carried out on all blood that is collected, on every visit, and before the plasma leaves the blood bank. Several aspects of the whole operation do not meet T.S. Regulations. For example, the transfusion needle is not inserted by a doctor, the donors are not screened for syphilis, more than 420 ml. blood is removed at one session, and a haematocrit and not a haemoglobin determination is made. However, it is hoped that the sub-committee will advise the licensing authority on the relevance of some of these requirements in the present context.

At the factory, plasma is pooled, and the pools contain plasma from as many as 6,000 donors. The fractionation process is carried out under excellent conditions in a modern, well-equipped plant. The personnel seemed highly competent and well-informed. My only criticism was that the aseptic filling area was small and overcrowded, and they placed too much reliance on laminar flow cabinets. However, a new filling area was due to be built within a matter of weeks.

Standardization of the Factor VIII concentrate is carried out using a house standard, and not the International Standard. They promised to mend their ways, but I am doubtful if they will, unless required to do so.

In conclusion, obviously the main problem with this product is the hepatitis hazard. The donors do not inspire confidence, and Factor VIII concentrate is prepared from very large plasma pools. Despite the HAA testing, the risk of hepatitis must still be considered to be present. However, the firm make no attempt to disguise this potential hazard.

D.P.T.