R. Schwartz

THE BIOLOGICAL BULLETIN

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Marketing Bulletin 9-83
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CLINICAL RESEARCH

QUALITY CONTROL OF PLASMA VS. HEAT TREATMENT

Earlier this year Cutter Laboratories intensified its plasma donor screening program in response to increasing medical concern over AIDS. This intensification keeps the emphasis on providing quality product squarely where it belongs. By eliminating potential unhealthy and hepatitis B positive donors, Cutter has traditionally reduced the risk of transmission of serious disease agents through blood products.

With the initiation on March 1, 1983 of additional screening procedures to reduce the possibility that AIDS may potentially be transmitted through certain blood products (see appendix I), Cutter has reinforced its existing program of donor screening to assure that the raw material for its quality plasma products continues to be of high quality. This approach is in keeping with the philosophy of Good Manufacturing Practices which holds that quality safeguards to control the quality of starting material are preferred to procedures to remove and reduce risk at a later point in manufacturing.

There is, for example, no known method acceptable for manufacture of coagulation factor products intended for human use which will inactivate the hepatitis B virus. Even the Hyland Hemophil T package insert (appendix III) states this in several places (see boxes and underlined sentences in appendix III).

In the area of research and development and in manufacturing, Cutter is working intensively to develop and refine a process which will exclude from Factor VIII concentrates not only the hepatitis B virus but any other disease transmitting agents which may be present in blood plasma. These efforts, as well as the efforts of other manufacturers, are hampered by the fact that it is not known whether or not AIDS is caused

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by a transmissible agent and whether or not that agent is present in blood. As a result, any actions taken to refine the manufacturing process to exclude such transmissible agents -- such as heat-treatment or chemical inactivation -- cannot yet be proven to be effective. In fact, it has been shown by chimpanzee studies that heat-treatment by itself is not sufficient to inactivate the hepatitis B virus in Factor VIII concentrates. This is confirmed in appendix II which is part of a brochure on heat-treated AHF produced by Hyland. (A similar product, manufactured in Germany, has never been tested this thoroughly to determine the degree of risk of hepatitis transmission).

As a result of the lack of positive evidence of complete inactivation of viruses, an assumption of increased protection from viral transmission from heat-treated Factor VIII concentrate is not warranted at this time.

In the meantime, it is our feeling that it would be of questionable value for hemophilia patients to be persuaded to change to products which raise the cost of an already expensive therapy in return for no guarantee of increased protection. It would also be inadvisable for hemophiliacs to suspend or reduce treatment and thus increase the probability of bleeding episodes which may result in disability and death.

As long as the AIDS agent is not known and as long as viral inactivation procedures cannot be shown to be effective, it is more feasible to prevent the introduction of a possible AIDS agent in the starting material than to attempt to eliminate it at a later stage of the process.

In summary, then, the following points are of interest:

- Cutter carefully screens plasma donors to eliminate donations from unhealthy individuals and "high risk" AIDS and hepatitis groups. (see appendix I)

- No known method compatible with production of coagulation factor plasma products for human use is effective in inactivating the hepatitis B virus. (see appendix II)

- Cutter is working diligently to discover a means of viral inactivation which can be applied to plasma products. Until such a method can be

devised, controls to assure the high quality of the raw material -- plasma -- are more effective in preventing disease transmission than any current process modification.

- Remember above all that it is not known whether AIDS can be transmitted by blood and certain blood products. This is speculative, controversial, and even contradicted by some data. Cutter, nevertheless, in order to avoid any possible risk, however remote, to its customers, has deliberately chosen to act on the assumption that AIDS may possibly be transmitted by certain blood products.

Attached are copies of the guidelines which were followed to establish additional screening procedures to eliminate "high risk" donors (appendix I). Also attached are statements from the Travenol Hemophil T brochure (appendix II) and package insert (appendix III) showing that Hemopil T -- although heat-treated -- still can transmit hepatitis.

Remember if hepatitis cannot be eliminated by heat-treatment, there is no assurance that any other viruses are inactivated by this process.

GRO-C

Merrill Boyce, Ph.D.
Cutter International

MTB/cfg

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Bethesda, MD 20205

March 24, 1983

FROM: Director, Office of Biologics,
National Center for Drugs and Biologics

SUBJECT: Recommendations to Decrease the Risk of Transmitting Acquired Immune Deficiency Syndrome (AIDS) from Plasma Donors

TO: All Establishments Collecting Source Plasma (Human)

The Acquired Immune Deficiency Syndrome (AIDS) has caused serious concern because of the implications for recipients of plasma derivatives if this disease is proven to be transmissible by blood or blood products. The major organizations involved in plasma collection have reached a consensus as to appropriate steps which should be taken to decrease the potential of blood or plasma donation by individuals who might be at increased risk of transmitting AIDS. Consistent with the recommendations of the American Blood Resources Association, the American Red Cross, the American Association of Blood Banks, the Council of Community Blood Centers, and the Public Health Service Interagency Committee, (copy attached), the Office of Biologics is advising that the following steps should be taken by all establishments collecting Source Plasma (Human):

1. Educational programs should be instituted to inform persons at increased risk of AIDS that until the AIDS problem is resolved or definitive tests become available, they should refrain from routine plasma donation because of the potential risk to recipients of certain plasma derivatives. As presently defined, persons at increased risk include those with symptoms and signs suggestive of AIDS, sexually active homosexual or bisexual men with multiple partners, Haitian entrants to the United States, present or past abusers of intravenous drugs* and sexual partners of individuals at increased risk of AIDS. Each Source Plasma donor should receive information about AIDS including the need for individuals at increased risk to voluntarily exclude themselves from routine plasma programs.

2. If plasma is collected from a donor belonging to any of the groups at increased risk, a label should be affixed to each unit to restrict its use in accordance with 21 CFR 606.120(b)(6). The recommended label statements are "CAUTION: For Use in Manufacturing Albumin, PPF, or Globulin Only" or "CAUTION: For Use in Manufacturing Noninjectable Products Only". HBsAg positive plasma is already subject to special labeling and shipping restrictions and these programs are not affected by this memorandum.

*Such intravenous drug abusers are already excluded by existing regulations.

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3. Re-education of personnel responsible for donor screening should be conducted with special attention to identifying the early signs and symptoms of AIDS in donors. The donor medical history should include specific questions designed to detect possible AIDS symptoms or exposure to patients with AIDS. Standard Operating Procedures (SOP) should be revised to include questions which elicit a history of night sweats, unexplained fevers, unexpected weight loss, or signs of lymphadenopathy or Kaposi's sarcoma.

4. Donors should be examined for lymphadenopathy. The initial and annual physical should provide an opportunity for an examination by the physician for generalized lymphadenopathy, while a more limited examination should be performed by an adequately trained individual on each donor on the day of plasma collection and a record made of the results of the examination.

5. An accurate record of each source plasma donor's weight prior to each donation should be made to permit ready identification of any unexplained weight loss. Any significant, unexplained decrease in weight should be considered cause for referral of the donor to a physician for complete evaluation prior to any further plasma collection. Any plasma in storage, which was previously collected from such a donor, should be quarantined until the physician's evaluation is completed.

6. The SOP should inform the staff that any products collected from a donor known or suspected to have AIDS should be considered potentially highly infectious and must be immediately quarantined and disposed of expeditiously and appropriately unless designated for investigative use related to AIDS. If not destroyed, such products must be labeled, stored and shipped in accordance with the standard procedures for handling infectious materials. Appropriate disposal procedures include autoclaving or controlled incineration; overwraps are required to protect staff in case of breakage.

Approved procedures developed by one of the major organizations such as the American Blood Resources Association, the American Red Cross, the American Association of Blood Banks and the Council of Community Blood Centers may be referenced in the licensed establishment's SOPs without individual submission to the Office of Biologics. Alternatively, licensed establishments which develop their own procedures should submit them to the Office of Biologics for approval concurrent with implementation. Revised labeling for plasma collected from high risk donor groups and intended for further manufacture of plasma derivatives should be submitted to the Office of Biologics (HFN-825).

This memorandum is intended to be an interim measure to protect recipients of blood and blood products until specific laboratory tests are available.

GRO-C

John C. Petricciani, M.D.

Attachment

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Response of chimpanzees to inoculation of AHF which contained added 300 CID of HBV. Serum alanine aminotransferase is plotted with the bar indicating one standard deviation for the eight preinoculation values.

Figure 2A

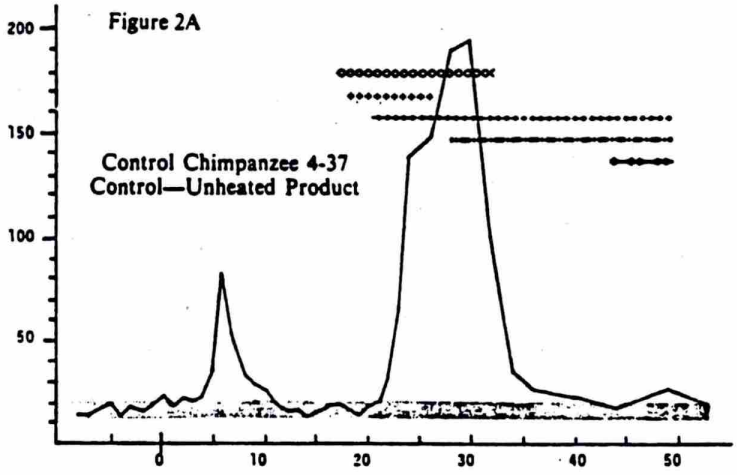


Figure 2B

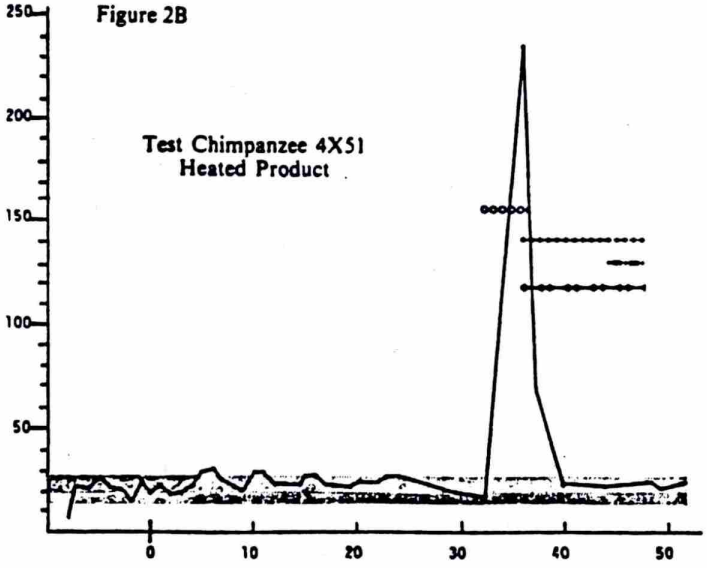
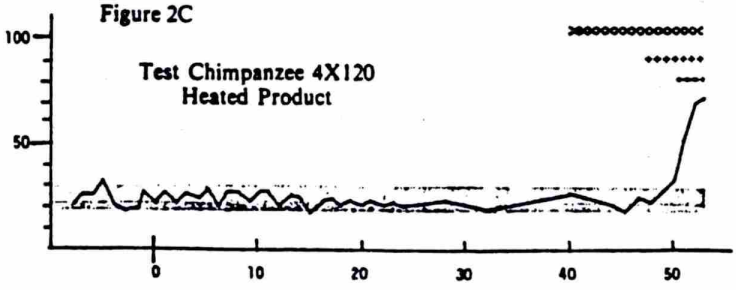
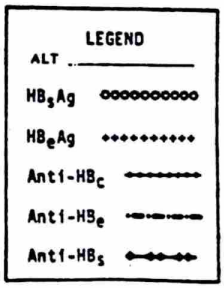


Figure 2C





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Response of chimpanzees inoculated with AHF containing 30,000 added CID of HBV. Serum alanine aminotransferase is plotted with the bar indicating one standard deviation for the eight preinoculation values.

Figure 3A

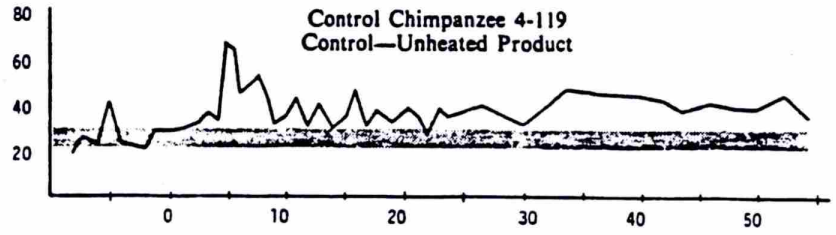


Figure 3B

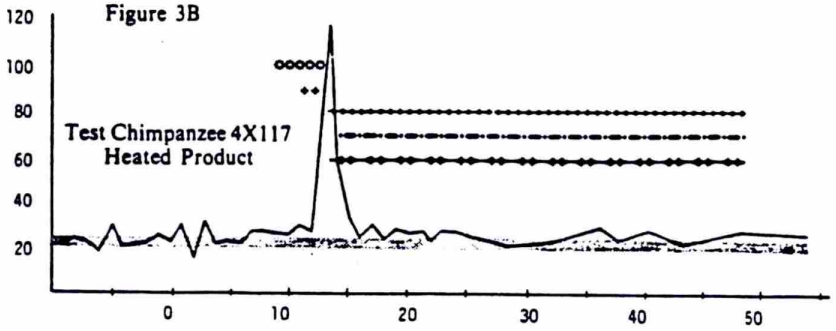
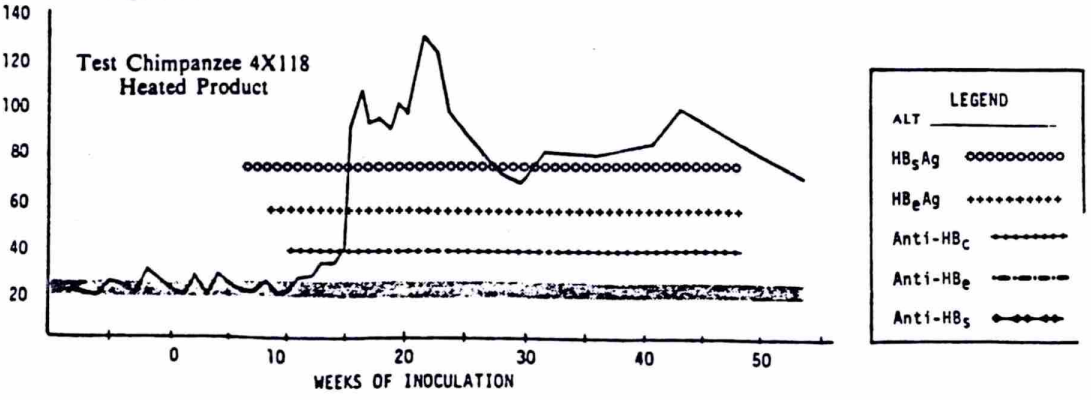


Figure 3C



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ANTIHEMOPHILIC FACTOR (HUMAN)
Method Four, Dried Heat-Treated HEMOFIL® T

The potency of each lot of this product is given on the container and package labels. See instructions given under DOSAGE AND ADMINISTRATION and "Rate of Administration" for potency-related administration instructions.

DESCRIPTION

Antihemophilic Factor (Human), Method Four, Heat-Treated, HEMOFIL® T,* is a sterile, stable, dried preparation of antihemophilic factor (Factor VIII, AHF, AHG) in concentrated form. It is prepared from fresh-frozen human plasma. The product also contains a trace amount of heparin, 1.0 unit (0.010 mg) or less per ml of reconstituted material, as a stabilizing agent. Concentrations of heparin many times greater than this have been shown[1] to have no demonstrable effect after infusion of the volumes encountered in the use of this product.

Antihemophilic Factor (Human), HEMOFIL® T, offers many advantages, the most significant of which are:

(1) Because it contains higher AHF potency than cryoprecipitate preparations with relatively small amounts of fibrinogen and other proteins, adequate AHF can be furnished with lower volumes of infused material.

(2) Each lot is assayed and labeled for its AHF content expressed as International Units of AHF activity. This permits estimation of dose needed and prediction of effect when compared to the variability of AHF content in cryoprecipitate preparations.

(3) Because of the predictable effect, therapy may be managed without repeated determinations of AHF levels. This is especially important when the patient is very young, when the patient's veins are poor, or when laboratory service is not readily available.

(4) AHF is very stable in the dry form.

Antihemophilic Factor (Human) is to be administered only by the intravenous route.

A change has been made in the manufacture of this product to include a heating step designed to reduce the risk of transmission of hepatitis. No procedure has been shown to be totally effective in removing hepatitis infectivity from Antihemophilic Factor (Human). (See section on CLINICAL PHARMACOLOGY.)

*Product and/or its manufacture covered by U.S. Patents Nos. 3,415,804, 3,631,018 and Reissue 29,698 (formerly U.S. Patent 3,803,115); patent pending.

CLINICAL PHARMACOLOGY

Antihemophilic factor (AHF) is a protein found in normal plasma which is necessary for clot formation. The administration of Antihemophilic Factor (Human), HEMOFIL® T, provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect of patients with hemophilia A (classical hemophilia).

The half-life of AHF administered to hemophiliacs has been variously estimated at 8 to 24 hours.[2-6] In the severe hemophiliac, 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."

An assessment of the efficacy of the heating step employed was performed by administration to chimpanzees of Antihemophilic Factor (Human) inoculated with 300 and 30,000 infectious units of hepatitis B. While there was no effect of heating on the high dose inoculum, the chimpanzees receiving 300 infectious units did not develop hepatitis B markers until 7½ and 10 months had elapsed, as compared to 4 months for untreated material, which may indicate a reduction in infectivity of the product for hepatitis B. The study also indicated that the heat treatment eliminated an unknown quantity of at least one type of non-A, non-B hepatitis virus present in the administered Antihemophilic Factor (Human).[7]

In addition to the chimpanzee study described above, the effectiveness of the heating step was also assessed by *in vitro* viral inactivation studies using, as a marker, a virus which is not commonly found in plasma. When known quantities of Sindbis virus were added to the product, it was shown that the heat treatment employed was capable of inactivating approximately 3.2 logs of this virus.

INDICATIONS AND USAGE

The use of Antihemophilic Factor (Human), HEMOFIL® T, is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.

The concentrate can be of significant therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per ml.[8] However, in such uses the dosage should be controlled by frequent laboratory determinations of circulating Factor VIII.

APPENDIX III - PAGE 1

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Antihemophilic Factor (Human) is not indicated in von Willebrand's disease.

CONTRAINDICATIONS

None known.

WARNINGS

This concentrate is prepared from large pools of fresh human plasma which may contain causative agents of viral hepatitis. However, each unit of plasma used in the manufacture of this product has been found to be nonreactive for hepatitis B surface antigen (HBsAg) when tested with licensed third generation reagents. In addition, this product has been subjected to a heating procedure during its manufacturing process designed to reduce the risk of transmission of hepatitis. Although these testing and heating steps reduce the risk of hepatitis transmission, the possibility of such transmission should be considered in use of the product.

PRECAUTIONS

General

This Antihemophilic Factor (Human) preparation contains blood group isoagglutinins (anti-A and anti-B). When large or frequently repeated doses are needed, as when inhibitors are present or when pre- and post-surgical care is involved, patients of blood groups A, B, and AB should be monitored for signs of intravascular hemolysis and decreasing hematocrit values. Hemolytic anemia, when present, may be corrected by the administration of compatible Group O Red Blood Cells (Human).

Identification of the clotting deficiency as one of Factor VIII is essential before the administration of Antihemophilic Factor (Human) is initiated.

Since Antihemophilic Factor (Human), Method Four, Heat-Treated, HEMOFIL® T, contains small residual amounts of fibrinogen which tend to cause the ground surface of glass to stick, plastic (disposable) syringes should be used.

Laboratory Tests

Although dosage can be estimated by the following calculations, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

If the AHF level fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected. By appropriate laboratory procedures, the presence of AHF inhibitor can be demonstrated and quantitated in terms of AHF units neutralized by each ml of plasma or by the total estimated plasma volume. After sufficient dosage to neutralize inhibitor, additional dosage produces predicted clinical response. It should be noted that when inhibitor is present, measurement of Lee-White clotting time may be a better index of adequacy of dosage than measurement of circulating AHF.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Antihemophilic Factor (Human). It is also not known whether Antihemophilic Factor (Human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Antihemophilic Factor (Human) should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Allergic reactions may be encountered from the use of AHF concentrate preparations.

DOSAGE AND ADMINISTRATION

Each bottle of Antihemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL® T, is labeled with the number of AHF units which it contains, 1 AHF unit being defined as the activity present in 1 ml of normal pooled human plasma less than 1 hour old (100% AHF level). The stated potency is expressed in International Units of AHF activity and is based upon the use of a standard traceable to the World Health Organization International Standard for blood coagulation Factor VIII (Human).

NOTE: The accompanying bottle of Sterile Water for Injection, U.S.P., contains a slight overfill. To obtain the total activity contained in the product when reconstituted according to instructions given under "Reconstitution," the entire injectable volume must be administered.

Abildgaard, *et al*[9] reported that infusion of 1 unit of AHF per kg body weight consistently produces an increase of 2% (of normal), while Shanbrom and Thelin[10] found that 3.8 to 4.0 units per kg produce an increase of 10% (of normal) in AHF level. (The former authors worked with boys 8 months to 14 years of age, while the latter worked primarily with adults.) The following formulas can therefore be used to calculate, approximately, the expected response from a given dose or the dose required for a given effect:

APPENDIX III, PAGE 2

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I. Units required =
body weight (in kg) X 0.4 X
desired AHF increase (in % of normal)

Example: 70 X 0.4 X 50 = 1,400 units

II. Expected AHF increase (in % of normal) =
$$\frac{\text{units administered}}{\text{body weight (in kg) X 0.4}}$$

Example: $\frac{1,400}{70 \text{ X } 0.4} = 50\%$

The data of Abildgaard, *et al* would call for a factor of 0.5 instead of 0.4 in the preceding formulas.

The amount of AHF that a hemophiliac requires for normal hemostasis varies with circumstances and with the patient. The amount of factor to be supplied will depend on the degree of deficiency and on the AHF level desired.

Kasper has found that minor hemorrhagic episodes will generally subside with a single infusion if a level of 30% or more is attained. For more serious hemorrhages, a Factor VIII level of 35 to 50% of normal should be obtained for optimum clot formation. In surgery, Kasper recommends that the first dose of Factor VIII, to achieve a level of 80 to 100%, be given an hour before the procedure. A second dose of Factor VIII half the size of the priming dose should be given about 5 hours after the priming dose. If several units of blood were lost during the operation, a third dose of concentrate should be given when the patient reaches the recovery room. The Factor VIII level should be maintained at a daily minimum of at least 30% for a healing period of 10 to 14 days.[11]

The preceding dosage formulas are presented as a reference and a guideline. Other dosage regimens have been proposed such as that of Hilgartner,[12] which outlines dosage according to the various types of bleeding episodes, and Schimpf, *et al*,[13] which describes continuous maintenance therapy.

Exact dosage determinations should be made based on the medical judgement of the physician regarding circumstances, condition of patient, degree of deficiency, and the desired level of Factor VIII to be achieved.

Reconstitution

1. Bring Antihemophilic Factor (Human), HEMOFIL® T, (dry concentrate) and Sterile Water for Injection, U.S.P., (diluent) to room temperature.
2. Remove caps from concentrate and diluent bottles to expose central portion of rubber stoppers.
3. Cleanse stoppers with germicidal solution.
4. Remove protective covering from one end of double-ended needle, using care not to touch the exposed end. Insert exposed needle through *diluent* stopper.
5. Remove protective covering from other end of double-ended needle, using aseptic technics as above. Invert diluent bottle over the upright concentrate bottle, then *rapidly* insert free end of the needle through the concentrate bottle stopper at its center. Vacuum in concentrate bottle will draw in diluent.
6. Disconnect the two bottles by removing needle from concentrate bottle stopper. *Shake vigorously for 5 seconds*, then agitate or rotate concentrate bottle until all material is dissolved. *Be sure that concentrate is completely dissolved; otherwise, active material will be removed by the filter.*

NOTE: Do not refrigerate after reconstitution.

Rate of Administration

Preparation of Antihemophilic Factor (Human), HEMOFIL® T, containing 34 or more AHF units per ml must be administered at carefully controlled rates: *i.e., a maximum administration rate of 2 ml per minute.* Accordingly, the administration of a 30-ml total volume containing 34 or more AHF units per ml must be evenly regulated over a period of 15 or more minutes. AHF preparations containing less than 34 AHF units per ml can be given rapidly, at a rate of 10 to 20 ml over a 3-minute period, with no significant reactions.

As a precautionary measure, the physician should determine the pulse rate before and during administration of the AHF concentrate. Should a significant increase of pulse rate occur, reduce the rate of administration or discontinue.

Administration

When reconstitution of Antihemophilic Factor (Human), HEMOFIL® T, is complete, the solution should be administered promptly (within 3 hours).

The reconstituted material should be at room temperature during administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

APPENDIX III PAGE 3

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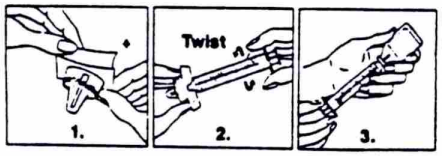
1. After reconstituting the concentrate as described under "Reconstitution," open the filter spike package by peeling back the label of the blister pack. (See Figure 1.)

2. Hold the clear plastic blister pack at the rim of the filter spike and aseptically attach the filter spike to an empty plastic syringe. Twist the filter spike onto the syringe to ensure a secure connection. (See Figure 2.)

3. Insert spike through the concentrate bottle stopper, inject air, and withdraw the reconstituted material into the syringe. (See Figure 3.)

4. Remove and discard the filter spike from the syringe; attach a suitable needle and inject intravenously.

5. **NOTE: Discard each filter spike after a single use.** If the same patient is to receive more than one bottle of concentrate, the contents of two bottles may be drawn into the same syringe through filter spikes before attaching the vein needle.



HOW SUPPLIED

Antihemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL® T, is furnished with a suitable volume of Sterile Water for Injection, U.S.P., a double-ended needle, and a filter spike.

The number of International Units of AHF activity, as determined for each lot, is stated on the label of each bottle.

Antihemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL® T, is processed and tested in accordance with requirements established by the Food and Drug Administration and is distributed under U.S. License No. 140.

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STORAGE

Antihemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL® T, should be stored under ordinary refrigeration (2° to 8°C, 35° to 46°F). Freezing should be avoided as breakage of the diluent bottle might occur.

Antihemophilic Factor (Human), HEMOFIL® T, may be stored for up to 6 months within the dating period at room temperature, not to exceed 30°C (86°F).

APPENDIX III, PAGE 4

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