# Summary of Basis for Approval

**Reference Number:** **98-0137**

**Drug Licensed Name:** **Antihemophilic Factor (Recombinant)**

**Manufacturer:** **by Pharmacia & Upjohn AB for Genetics Institute, Inc.**

**Drug Trade Name:** **ReFacto®**

## I. Indication for Use

ReFacto®, Antihemophilic Factor (Recombinant), is indicated for the control and prevention of hemorrhagic episodes and for surgical prophylaxis in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia). ReFacto® is indicated for short-term routine prophylaxis to reduce the frequency of spontaneous bleeding episodes. The effect of regular routine prophylaxis on long-term morbidity and mortality is unknown.

ReFacto® can be of a significant therapeutic value for treatment of hemophilia A in certain patients with inhibitors to factor VIII. In clinical studies of ReFacto®, patients who developed inhibitors on study continued to manifest a clinical response when inhibitor titers were < 10 Bethesda Units (BU)/ml. When an inhibitor is present, the dosage requirement of factor VIII is variable. The dosage can be determined only by a clinical response and by monitoring of circulating factor VIII levels after treatment.

ReFacto® does not contain von Willebrand factor and therefore is not indicated in von Willebrand's disease.

## II. Dosage Form, Route of Administration and Recommended Dosage

### A. Dosage Form

ReFacto® is a sterile, non-pyrogenic, lyophilized powder for injection available in nominal dosage strengths of 250, 500 and 1000 International Units (I.U.) per vial. One International Unit is the amount of factor VIII activity present in one ml of pooled, normal human plasma. Potency, in I.U., is determined using the European Pharmacopeial chromogenic assay against the World Health Organization International Standard for factor VIII concentrates.

After reconstitution of the lyophilized powder with 4 ml of —— Sodium Chloride solution, the 250, 500 and 1000 nominal dosage strengths of ReFacto® are comprised of approximately 62.5 I.U./ml, 125 I.U./ml and 250 I.U./ml, respectively. Each of the dosage strengths is comprised of approximately ——— sodium chloride, ——— sucrose, ———, L-Histidine, ——— calcium chloride, ——— and ——— polysorbate 80, ———.

The lyophilized formulation contains no preservatives, nor any added human components.

## B. Route of Administration

ReFacto® is administered only by intravenous infusion (IV) within 3 hours after reconstitution of the lyophilized powder with —— Sodium Chloride solution (provided).

## C. Recommended Dosage

Treatment with ReFacto®, as for all factor VIII products, should be initiated under the supervision of a physician.

Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Doses administrated should be titrated to the patient's clinical response. In the presence of an inhibitor, higher doses may be required.

The calculation of the required dosage of factor VIII is empirically based. On average, one I.U. of ReFacto® per kilogram of body weight is expected to increase the circulating activity of factor VIII by approximately 2 I.U./dl. The required dose is determined using the following formula:

**No. of factor VIII I.U. required = body weight (kg) x desired factor VIII rise (I.U./dl) x 0.5 I.U./kg per I.U./dl.**

Clinical studies have shown that elimination half-life for ReFacto® and Hemofil® M, a plasma-derived Antihemophilic Factor, were not significantly different. Mean incremental recovery was also comparable (see **Pharmacokinetics** under **Medical**). Patients may expect to use the same dose of ReFacto® on an I.U. basis as that used with other factor VIII preparations, either recombinant or plasma-derived.

Precise monitoring of the replacement therapy by means of coagulation analysis (plasma factor VIII activity) is recommended where appropriate, particularly for surgical intervention.

The product is labeled on the basis of the chromogenic assay. The available clinical trial data suggest either the one-stage clotting assay or the chromogenic assay may be used to help follow patients clinically. Most clinical trial subjects were monitored with the one-stage clotting assay. It must be noted the one-stage clotting assay yields results, which are lower than the values obtained with the chromogenic assay.

For short-term routine prophylaxis to prevent or reduce the frequency of spontaneous musculoskeletal hemorrhage in patients with hemophilia A, ReFacto® should be given at least twice a week. In some cases, especially pediatric patients, shorter dosage intervals or higher doses may be necessary. In clinical studies in previously treated patients [PTPs] (ages 8-73 years) and previously untreated patients [PUPs] (ages 9-52 months), the mean dose used for routine prophylaxis was 27±10 IU/Kg and 57±20 IU/Kg, respectively. Pharmacokinetic/pharmacodynamic modeling undertaken by the sponsor predicts that substantially fewer (~47%) total bleeding episodes (spontaneous and traumatic) might be associated with routine prophylactic dosing of PTPs with 50 IU/kg 3 times per week, as compared to dosing with 25 IU/kg 2 times per week. However, no randomized controlled data comparing bleeding frequency during routine prophylaxis using different dosing schedules are available (see sponsor phase IV commitments).

## III. Manufacturing and Controls

### A. Manufacturing

The active substance in ReFacto® is Antihemophilic Factor (Recombinant), a 1438 amino-acid glycoprotein (approximately 170 kDa) that is produced in engineered Chinese hamster ovary (CHO) cells. The active substance in ReFacto® differs from other factor VIII preparations (recombinant and plasma derived) in that the [redacted] The production cells were [redacted]

The structure of ReFacto® has been extensively studied by state-of-the-art techniques and was compared to the structure of plasma-derived factor VIII and to the 90 + 80 kDA complex isolated from human plasma. These studies indicate that ReFacto® and the 90 + 80 kDa form of plasma factor VIII have many comparable structural characteristics.

A production campaign begins by thawing an ampoule of production cells maintained in a Working Cell Bank (WCB), expanding the culture in spinner flasks and seed reactors and finally in a ——————. Cell culture is operated in a continuous perfusion mode.

The production cell line has been adapted in defined growth medium that contains Human Serum Albumin (HSA) and recombinant human insulin. The Master Cell Bank (MCB) and WCB have been ——————
——— in the absence of human or animal serum.

ReFacto® is purified from the culture medium by means of a five-step chromatography process, including ——————
——————— The purification process also contains a ——— virus inactivation step capable of reducing viral burden.

The active substance and drug product are manufactured at the Pharmacia & Upjohn AB facility in Stockholm, Sweden. Pharmacia & Upjohn AB also tests the final containers for sterility and particulates, labels and packages the product, and ships the released product to distribution centers.

Drug product testing includes potency, protein concentration, specific activity, SDS-PAGE (identity), SEC-HPLC (aggregates and fragments), sterility, endotoxin, appearance (before reconstitution), dissolution time and appearance (coloration and clarity after reconstitution), residual moisture, pH, and concentrations of the major excipients.

The specific activity of ReFacto is 11,200-15,500 IU per milligram of protein. ReFacto is not purified from human blood and contains no preservatives or added human components in the final formulation.

## B. Validation

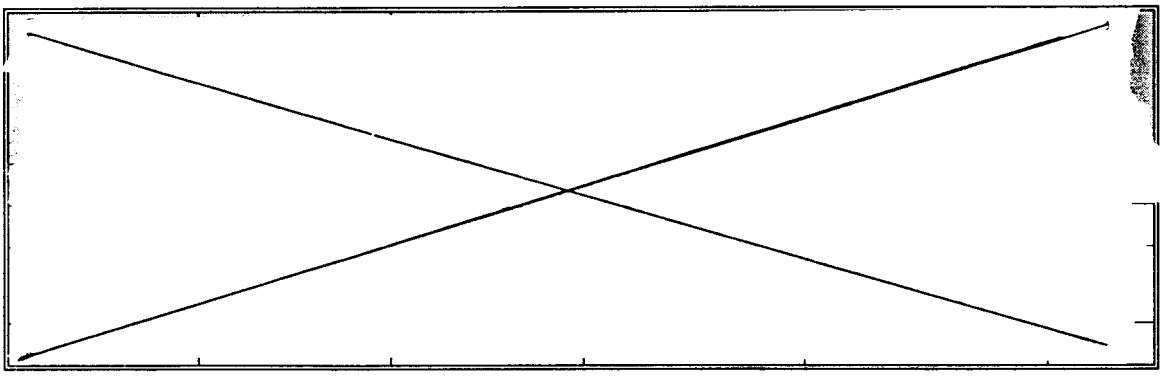
The production cell line has been cryopreserved as an MCB, from which a WCB has been derived. The MCB, the WCB, and end-of-production cells have been characterized and found to be stable in genotype and free of any detectable bacterial, mycoplasmal, or fungal contamination. No adventitious virus was detected from a conventional testing program.

The manufacturing process for ReFacto® has been validated for consistency, robustness and for removal of impurities. In particular, validation studies have been accepted in lieu of lot-by-lot testing of active substance and drug product to establish the removal of certain defined contaminants. These validation studies include removal of ——————
——————
——————, and have indicated that each of

these potential contaminants is reproducibly removed to acceptable levels in the final drug product. Although validation studies showed that ——— ——————— are reproducibly removed to low levels, these impurities are monitored ———————

Assays of the active substance and drug product have been validated for accuracy, precision and reproducibility. All drug product lots have been shown to conform to requirements for identity, purity, potency and sterility according to 21 CFR Part 610. — conformance lots have been submitted to CBER for testing and have been shown to meet the testing requirements.

Various steps in the purification process have been validated for their ability to remove viruses that may not have been detected in the production cells. Two of the chromatography steps ( ——————————— ) and the solvent detergent step were evaluated using appropriate model viruses ( ——————————————————————— ——————————————————————— ). Overall, the purification process has been shown to reduce these viruses by a factor of at least $10^7$.



No testing, or purification validation, has been carried out for Bovine Spongeform Encephalopathy (BSE). Neither bovine components nor bovine serum is used in the cell culture manufacturing process. Those components used in the development of the cell line up to cell banking, such as fetal bovine serum, were sourced from countries known to be free from BSE. Thus, the possibility of introduction of BSE into the ReFacto® manufacturing process is considered to be negligible. ———————————

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## C. Stability

The stability of the active substance has been investigated in three batches for up to 18 months. Data to date indicate that the active substance is stable for 18 months when maintained at -70 °C.

The stability of the drug product has been investigated in six lots of 250-I.U., five lots of 500-I.U., and five lots of 1000-I.U. Data to date indicate that the drug product is stable for 24 months when maintained at 2-8 °C. The drug product is also stable for 3 months at room temperature. Although studies of the reconstituted material have indicated that it is stable for at least 12 hours at room temperature, it should be administered within 3 hours of reconstitution to assure aseptic use.

ReFacto® is a light-sensitive product. A statement that the product is light-sensitive and should be protected from light is included in the User Package Insert, as well as the vial label and final outer package.

## D. Labeling

The package insert, container, and package labels are in compliance with 21 CFR 201.57, 610.60, 610.61, and 610.62. The trademark, ReFacto®, is not known to be in conflict with the trademark of any other biological product.

## E. Establishment Inspection

A pre-approval inspection (PAI) was conducted at the Pharmacia & Upjohn AB facility located in Stockholm, Sweden in October 1998 by inspectors from Center for Biologics Evaluation and Research and Office of Regulatory Affairs, FDA. The ReFacto® production facilities at Pharmacia & Upjohn AB in Stockholm, Sweden are the only manufacturing sites for both the active substance and the finished ReFacto® product, and were the subject of the inspection. The establishment was found to be in compliance with current good manufacturing practices. However, following commitments were made:

1). Implementation of US licensed plasma in the manufacture of cell culture human serum albumin at the Pharmacia & Upjohn AB facility in Stockholm, Sweden so that finished product will be available [redacted].

2). Submission of updates on the ongoing validation studies for column resin life span by May 2000. Concurrent studies will include conductivity and total organic carbon (TOC) testing to evaluate the effectiveness of column regeneration.

3). Introduction of sterilizable spray bottles for ———— sanitization in environmentally classified areas.

4). Revision of the procedure for manual inspection of freeze-dried products (SOP 6017-05-OFI) to reduce the total acceptable defect level in ReFacto® ———— Critical and non-critical defect limits will be reduced to reflect historical levels.

A copy of the inspection report and the inspectional closeout memorandum are on file.

### F. Environmental Assessment

A report of the impact on the environment is included in the license application. ReFacto® is manufactured in compliance with applicable federal, state, and local environmental regulations. No significant effects on the environment are expected to result from the manufacture or use of this product. A Finding of No Significant Impact is attached.

Additionally, if this application had been prepared at a later date, Genetics Institute, Inc. could have requested, and would have been granted, a categorical exclusion under 21 CFR 25.31 (c).

## IV. Pharmacology and Toxicology

The safety, toxicity, efficacy, and absorption, distribution, metabolism, and elimination (ADME) of ReFacto® have been tested in animals.

### A. Pharmacology

ReFacto® exhibits interactions with von Willebrand Factor (vWF), cofactor activities in the activation of factor X to Xa, as well as activation and inactivation profiles with thrombin and Protein C, which are comparable to plasma-derived factor VIII.

ReFacto® and plasma-derived factor VIII (Octonativ-M®) had similar binding to canine vWF and a similar efficacy in correcting the hemostatic deficiency in a canine model of hemophilia A as measured by whole blood clotting time, partial thromboplastin time, and toenail secondary bleeding time.

No effect on blood pressure, heart rate, respiration or electrocardiographic traces was observed in anaesthetized beagle dogs following a bolus intravenous dose of 500 I.U./kg of ReFacto®.

## B. Pharmacokinetics

After intravenous administration of ReFacto® and Octonativ-M® to hemophilia A dogs, the elimination half-life and mean residence time were similar, whereas differences were observed in clearance and volume of distribution.

After intravenous administration of ReFacto® and a non-proteolytically processed form of the protein (non-proteolytically processed 170 kDa) to cynomolgus monkeys, the activity time profiles and pharmacokinetic parameter estimates were similar, suggesting that any non-proteolytically processed 170 kDa protein in the final product should have no effect on the pharmacokinetics of ReFacto®.

ReFacto® is immunogenic in both rats and monkeys, and the antibody response resulted in neutralization of both the exogenous ReFacto® as well as the endogenous FVIII:C. In some of the monkey studies, the antibody response induced an acquired hemophilia syndrome which resulted in hemorrhages and changes secondary to hemorrhage. Similar effects were produced in monkeys receiving plasma-derived factor VIII (Octonativ-M®).

In the single and repeated dose intravenous toxicity studies in rats and monkeys, all findings were related to the immunogenicity of ReFacto®. In both species, the no-observed-adverse-effect-level (NoAEL) for non-immunogenic-related toxicities in the 4 week studies was ≥1250 I.U./kg/day.

Due to the formation of neutralizing anti-ReFacto® antibodies in animals, long-term studies were not considered feasible.

No local irritant effects were observed following repeated intravenous administration in rats and monkeys and single paravenous and intra-arterial administration in dogs.

No mutagenic activity was found in a mouse micronucleus test.

Based on the animal toxicology studies performed, the safety profile suggests that ReFacto® can be given to humans for the proposed indication with sufficient safety at the recommended dose regimen.

# V. Medical

A total of eleven clinical studies have been conducted, four of which were considered primary in evaluating the safety and efficacy of ReFacto®. The first study (9710751, CTN 95-R811-057), conducted in 18 patients, was a randomized, multi-center, three-way crossover, single-blind study comparing the

pharmacokinetics of two formulations of recombinant factor VIII ReFacto® and Hemofil® M. This study, conducted in the U.S. at 6 centers, is complete. Because the intended use of ReFacto is as a replacement therapy, this pharmacokinetic study received special review emphasis.

The second study (9710778, CTN 93-R831-013) and third study (9710641, CTN 93-R833-019) were designed to evaluate the long-term prophylaxis and/or on demand treatment of ReFacto® in PTPs and PUPs, respectively. These studies are ongoing.

The fourth study (99710781, CTN 95-R832-020) was a surgical prophylaxis study in which patients with factor VIII deficiency were enrolled if they were to undergo elective, major surgical procedures that required factor VIII replacement therapy. This study is complete.

FDA Inspections of two clinical sites in Europe were conducted in August 1998. Inspection of one clinical site in the United States occurred in September 1998. The sites were found to be in general compliance with current good clinical practices with regard to the ReFacto® clinical studies. However, some questions for the sponsor that arose as a result of the clinical site inspections were raised by the agency in its complete response letter of February 1, 1999, and were subsequently adequately answered by the sponsor in its amendment 016 to the BLA dated June 4, 1999.

A safety update was submitted May 13, 1999, reporting cumulative safety data as of July 31, 1998. Additional safety data through the cutoff date August 31, 1999 contained in the ReFacto IND Annual Report submitted January 31, 2000 was also reviewed.

## A. Pharmacokinetics

The crossover pharmacokinetic evaluation of two formulations of ReFacto® and Hemofil® M was performed at doses of 50 I.U./kg in 18 previously treated patients. The dosing of this study conformed to the guidelines published by the International Society on Thrombosis and Hemostasis. The two ReFacto® formulations were well tolerated and bioequivalence of the two formulations was established. A confidence interval analysis comparing the $AUC_{0\text{-infinity}}$ for Refacto to that of plasma-derived Hemophil® M did not establish bioequivalence because the $AUC_{0\text{-infinity}}$ of ReFacto was modestly higher (23.6 versus 20.7 IU*hr/ml, respectively). Elimination half-lives for ReFacto® and Hemofil® M were not significantly different (14.5± 5.3 hours, range 7.6 – 27.7 hours, and 13.7 ± 3.4 hours, range 8.8 – 23.7 hours, respectively). Mean incremental recovery (K-value) was also comparable (2.4 ± 0.4 I.U./dl per I.U./kg for ReFacto® and 2.3 ± 0.3 I.U./dl per I.U./kg for Hemofil® M).

In two additional clinical studies, pharmacokinetic parameters were evaluated for PTPs and PUPs. In PTPs (n=87), ReFacto had a mean incremental recovery of 2.4 ± 0.4 I.U./dl per I.U./kg (ranged from 1.1-3.8 I.U./dl per I.U./kg) and an elimination half-life (n=67) of 10.7 ± 2.8 hours. In PUPs (n=45), ReFacto had a lower mean incremental recovery of 1.7 ± 0.4 I.U./dL per I.U./kg (ranged from 0.2-2.8 I.U./dL per I.U./kg) as compared to PTPs. Population pharmacokinetic modeling using data from 44 PUPs led to a mean estimated half-life of ReFacto in PUPs of 8.0 ± 2.2 hours. These parameters did not change over time (12 months) for PTPs or PUPs.

## B. Previously Treated Patients

The efficacy of ReFacto® in PTPs with moderate or severe hemophilia A was assessed in an open-label study of on-demand, self-administered treatment and peri-operative use. The patients were not stratified according to the severity of the factor VIII deficiency, nor was any attempt made to directly compare ReFacto® with any other product. All endpoints were based on the subjective evaluation (Excellent, Good, Fair, None) by either the patient or the physician.

A total of 117 patients have been enrolled in the 9710778 study of whom 113 are included in the efficacy analysis. Forty-nine lots of ReFacto® were used in this study as of July 31, 1998. The subjects received a median of 230 injections (range 4-1530 injections) over a median of 1200 days (range 31-1640 days). The subjects experienced a median of 54 bleeding episodes during the study period. No patient reported "failure" of treatment with ReFacto®, however, one PTP discontinued ReFacto treatment and switched to another product after the development of inhibitors. Overall 71% (5201/7300) of bleeding episodes were treated successfully with one infusion. Seventeen percent of bleeding episodes was treated with 2 injections, and 5% were treated with 3 injections. There were few instances of progressive dose escalation in cases were multiple injections were administered. Of the infusions administered, 92% (10,723/11,655) were rated as providing an "Excellent" or "Good" response.

## C. Previously Untreated Patients

Study 9710641, CTN 93-R833-019 is a multicenter, open-label safety and efficacy study of ReFacto® in PUPs. Of the 99 patients enrolled in the study, all were treated successfully on an on-demand basis or for the reduction of bleeding episodes, except for two PUPs who discontinued ReFacto treatment and switched to another product after the development of inhibitors. The median number of bleeding episodes per subject was 12. In no case prior to the development of inhibitors was the efficacy rating "None" (no response).

## D. Surgery

In the surgical study, 28 procedures were performed in 25 patients at 19 clinical sites in the U.S. and Europe. Nineteen patients were PTPs (15 of these PTPs were included in the long-term on-demand/prophylaxis study) and six patients were infants included in the PUP study. Subjects were required to have moderate (plasma FVIII:C 2-5 I.U./ml) or severe (FVIII:C < 2 I.U./ml) hemophilia A. Three subjects received the concomitant antifibrinolytic agent, tranexamic acid and 3 subjects received a non-study Factor VIII product in addition to Refacto® at some point between postoperative days 2 to 90.

The mean plasma FVIII:C level following the pre-surgery ReFacto® dose was 1.28 I.U./ml, as measured by a central laboratory using the chromogenic assay. In all but 4 procedures in which therapy was monitored locally using the chromogenic assay, plasma FVIII:C activity was measured by the local laboratory using a one-stage clotting assay. The peri-operative values obtained by the local laboratories using the one-stage assay of FVIII:C for 18 PTPs were on average 27% less than the values obtained by the central laboratory using the chromogenic assay.

The median number of injections during the surgical and post-operative course was 41 (range 10-90). The two longest treatment periods were 57 and 68 days.

Hemostasis was judged as "Excellent" or "Good" after all 28 surgical procedures. The blood loss during the day of surgery was judged to be similar to what would be expected in patients without a coagulation disorder for the 26 procedures where assessments were made. The duration of post-operative wound site oozing was not required by the protocol to be recorded, and was not reported. Transfusions were required in two patients. One was a PTP patient with low hemoglobin levels who received 1 unit of red blood cells one day after surgery and the other was a PUP patient with low hemoglobin before surgery who received 1 unit of red blood cells.

The average preoperative dose for ReFacto® was 59 I.U./kg (range 20 to 250 I.U./kg); the average maintenance dose was 101 I.U./kg (range 32 to 300 I.U./kg); and the average weekly dose used in the week following surgery was 714 I.U./kg/week (range 220 to 2600 I.U./kg/week).

Circulatory factor VIII levels targeted to restore and maintain hemostasis were achieved. While the one-stage clotting assay was used most frequently in the surgical setting (24 versus 4 surgeries), hemostasis was maintained throughout the surgical period regardless of which assay was used. Procedures included orthopedic procedures, inguinal hernia repair, epidural

hematoma, evacuation, transposition ulnar nerve, and other minor procedures (e.g., venous access catheter placement and explantation, toenail removal).

## E. Prophylaxis

ReFacto® has been studied in short-term routine prophylaxis. In uncontrolled clinical trials, an average dose of 27 ± 10 I.U./kg in PTPs (n=77) and an average dose of 57 ± 20 I.U./kg in PUPs (n=17) was given repeatedly at variable intervals longer than 2 weeks. It should be noted that rounding up dosage calculations to the nearer whole vial of product tends to contribute to higher doses being used for PUPs. In 64 patients who had both "on demand" and prophylactic periods during their time on study, the mean rate of spontaneous musculoskeletal bleeding episodes was less during periods of routine prophylaxis. There was an average of 10 bleeding episodes compared to an average of 37 bleeding episodes per year during the "on demand" periods.

The clinical trial experience with routine prophylaxis in PUPs is limited (n=17). These non-randomized trial results should be interpreted with caution, as the investigators exercised their own discretion in deciding when and in whom prophylaxis was to be initiated and terminated.

## F. Safety

As of 31 July 1998, the clinical studies of ReFacto® had involved a total of 218 patients (117 PTPs including 4 who participated in the surgery study only, and 101 PUPs) who had received more than 84 million I.U. over 54 months.

During clinical studies with ReFacto®, 77 adverse reactions in 43 of 218 patients (20%) probably-or possibly related to therapy were reported for 64,363 infusions (0.12%). These were anaphylaxis (1), dyspnea (6), urticaria (1), nausea (11), headache (5), vasodilation (5), dizziness (4), permanent venous access catheter complications (3), asthenia (3), fever (3), taste perversion [altered taste] (3), bleeding/hematoma (3), infected hematoma (1), anorexia (2), diarrhea (2), injection site reaction (2), somnolence (2), rash (2), pruritus (2), angina pectoris (1), tachycardia (1), perspiration increased (1), chills (1), increased amino transaminase (1), increased bilirubin (1), pain in finger (1), muscle weakness (1), CPK increase (1), cold sensation (1), eye disorder-vision abnormal (1) coughing (1), myalgia (1), gastroenteritis (1), abdominal pain (1), acne (1), and forehead bruises (1).

A low-level inhibitor was detected in one of 113 previously treated patients (0.9%) after 107 exposure days to ReFacto®. At the time of inhibitor

detection, the patient also was diagnosed with monoclonal gammopathy of unknown significance.

Thirty of the 101 PUPs (30%) developed an inhibitor, 16 out of 101 (16%) with a high titer (≥ 5 B.U.) (11 of the 16 patients had peak values ≥ 10 B.U./ml) and 14 out of 101 (14%) with a low titer (< 5 B.U.). These results appear comparable to the results obtained for the other plasma-derived and recombinant factor VIII products.

Additional adverse experiences considered by both the investigator and sponsor as unlikely to be related to ReFacto® administration included dyspnea (3), rash (2), pruritis (1), neuropathy (1), arm weakness (1), and arm thrombophlebitis (1).

No viral seroconversions to HIV, HBV, or HCV were ascribed to exposure to the test product.

### G. Post-Marketing (Phase IV) Studies and Commitments

Genetics Institute has made following post-marketing (Phase IV) studies and commitments:

1). The commitment of February 29, 2000 to pre-clear with FDA educational material related to use of the one-stage and chromogenic assays

2). The commitment of March 2, 2000 to monitor hemostatic efficacy in 25 surgical cases (10 cases already studied plus an additional 15 cases) using the chromogenic assay at the local laboratory to measure factor VIII levels

3) · The commitment to provide a detailed protocol for a randomized trial using two different regimens for routine prophylaxis and submit a report to CBER containing the data and analyses on the feasibility of such a trial. If GI elects not to undertake such a randomized controlled trial in routine prophylaxis, the sponsor will make their assessment available to the public including the power analysis based on their pharmacokinetic/pharmacodynamic model.

## VI. Blood Products Advisory Committee

The labeled potency and potency during clinical trials of ReFacto® were determined using the European pharmacopeial chromogenic assay. It is noted that this assay is not the standard assay used in the United States and yields

results that are different from those of the one-stage clotting assay. On December 11, 1998, the Committee was asked to comment on how the discrepancy in assay results might affect dosing of ReFacto®. The committee voted (7 yes, 3 no with 1 abstention) that the information supplied in the dosage and administration section of the proposed package insert is sufficient to dose and monitor ReFacto® appropriately.

## VII. Package Insert

A copy of the approved package insert is attached.

3/31/2000
Andrew Chang, Ph.D. Date

L. Ross Pierce, M.D. 4/5/00
L. Ross Pierce, M.D. Date

Paul Aebersold 4/4/00
Paul Aebersold, Ph.D. Date

Martial D. Green
M. David Green, Ph.D. Date

3/31/00
Thomas Lynch, Ph.D. Date

3/31/00
Mark Weinstein, Ph.D. Date

4/4/00
Robert Darius Date

05-APR-00
Mary Padgett Date