Summary of Basis for Approval

STN: **125063/0**

Drug Licensed Name: **Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (rAHF-PFM)**

Manufacturer: **Baxter Healthcare Corporation**

Proprietary Name: **ADVATE**

I. Indication for Use

ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (hereafter referred to as ADVATE rAHF-PFM) is indicated in hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes. ADVATE rAHF-PFM is also indicated in the peri-operative management of patients with hemophilia A undergoing surgical procedures.

ADVATE rAHF-PFM can be of significant therapeutic value in patients with Factor VIII inhibitors not exceeding 10 Bethesda Units (BU) per mL. However, in patients with a known or suspected inhibitor to Factor VIII, the plasma Factor VIII level following product infusion should be monitored frequently and the dose of ADVATE rAHF-PFM should be adjusted accordingly.

ADVATE rAHF-PFM is not indicated for the treatment of von Willebrand's disease.

II. Dosage Form, Route of Administration and Recommended Dosage

A. Dosage Form

ADVATE rAHF-PFM is formulated as a sterile, non-pyrogenic, lyophilized cake of concentrated rAHF for intravenous injection and is provided in single-dose vials, which contain in each vial nominally 250 IU, 500 IU, 1000 IU or 1500 IU. Each vial of ADVATE rAHF-PFM is labeled with the actual AHF activity expressed in IU per vial. Biological potency is determined by an *in vitro* assay that employs a Factor VIII concentrate standard that is referenced to a World Health Organization International Standard for Factor VIII:C concentrates. The specific activity of ADVATE rAHF-PFM is 4,000 to 10,000 IU per milligram of protein.

When reconstituted with 5 mL of sterile water for injection, the 250 IU/vial, 500 IU/vial, 1,000 IU/vial and 1,500 IU/vial nominal potencies have concentrations of approximately 50 IU/mL, 100 IU/mL, 200 IU/mL, and 300 IU/mL, respectively. Each of the potencies contains approximately 10 mM histidine, 10 mM Tris, 90 mM sodium chloride, 0.010% (w/v) Tween-80, 3.2% (w/v) mannitol, 0.8% (w/v) trehalose, 0.08 mg/mL reduced glutathione, and 1.7 mM calcium chloride.

The final drug product contains no preservatives, nor any added human or animal components in the formulation. Recombinant von Willebrand Factor (rVWF) is co-expressed with ADVATE rAHF-PFM and helps to stabilize it in cell culture. The final product contains only trace amounts of rVWF, which will not have any clinically relevant effect in patients with von Willebrand's disease.

B. Route of Administration

ADVATE rAHF-PFM is administered only by intravenous infusion after reconstitution of the lyophilized powder with 5 mL sterile water for injection. As for all parenteral drug products, ADVATE rAHF-PFM should be inspected for particulate matter and discoloration prior to administration. ADVATE rAHF-PFM should be administered at room temperature not more than 3 hours after reconstitution. Plastic syringes must be used with this product since proteins such as ADVATE rAHF-PFM can adhere to the surface of glass syringes resulting in a potential loss of Factor VIII product to the patient.

A bolus dose of ADVATE rAHF-PFM should be administered over a period ≤ 5 minutes (maximum infusion rate, 10 mL/min).

C. Recommended Dosage

Treatment with ADVATE rAHF-PFM, 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 are likely to be required. Inhibitors present in high-titer (> 10 Bethesda Units (BU)) will likely require treatment with alternative products, as the continued use of ADVATE rAHF-PFM in the face of plasma inhibitor concentrations of this magnitude is unlikely to be effective and/or practical.

The calculation of the required dosage of Factor VIII is empirically based. On average, 1 IU of ADVATE rAHF-PFM per kilogram of body weight is expected to increase the circulating activity of Factor VIII by approximately 2 IU/dL.

The required dose for patients with < 1% of normal Factor VIII activity is determined using the following formula:

Dose (IU/kg) = Target Level (IU/dL) ÷ 2

When clinically appropriate, it is recommended that relevant laboratory tests, including Factor VIII assays, be performed on the patient's plasma at intervals to assure that adequate Factor VIII levels are achieved and maintained.

III. Manufacturing and Controls

A. Manufacturing

The active ingredient in ADVATE rAHF-PFM is a purified glycoprotein consisting of 2,332 amino acids that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line ----------. The cell line expresses both recombinant human Factor VIII and recombinant human VWF from the identical coding regions to those used for the currently licensed product, RECOMBINATE rAHF. There are no known changes in the promoter region of these sequences. This cell line has been adapted for production of ADVATE rAHF-PFM in a culture medium that does not contain additives of human or animal origin. Baxter Healthcare Corporation prepared the Master and Working Cell Banks (MCB and WCB, respectively).

ADVATE rAHF-PFM is expressed into the cell culture medium and is purified from the culture medium using a series of chromatography steps, including immunoaffinity chromatography with a monoclonal antibody directed against Factor VIII. The production process includes a dedicated, viral inactivation solvent-detergent treatment step. Physiochemical analysis demonstrated that the recombinant Factor VIII molecule in commercial-scale ADVATE rAHF-PFM is comparable to pilot-scale rAHF-PFM and RECOMBINATE rAHF.

ADVATE rAHF-PFM drug substance is manufactured at the Baxter Healthcare Corporation facility at ---------- Neuchâtel, Switzerland. The drug product is manufactured at the Baxter Healthcare Corporation facility at ----------. ADVATE rAHF-PFM contains no preservatives or added human or animal components in the final formulation. Final packaging/labeling takes place at the Baxter Healthcare Corporation facility at ----------. Baxter Healthcare Corporation tests the final containers for sterility and ----------, labels and packages the product, and ships the released product to distribution centers. Drug product testing includes determinations of potency, protein concentration, specific activity, sterility, ----------, appearance (before reconstitution), ---------- and appearance (coloration and clarity after reconstitution), residual moisture,

pH, and excipient levels, as well as ---------- (identity) and ----------

B. Validation

Utility systems, manufacturing equipment, manufacturing processes and analytical methodologies used in the production of ADVATE rAHF-PFM have been validated according to established written procedures. Procedures are in place to ensure routine maintenance of equipment and specified monitoring of environmental conditions and quality oversight within the production facilities.

The production cell line has been ---------- as a MCB, from which a WCB has been derived. The MCB, the WCB, and ---------- have been characterized and found to be stable in genotype and free of any detectable bacterial, or fungal contamination. No adventitious virus was detected from a conventional testing program. The manufacturing process for ADVATE rAHF-PFM 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 drug substance and drug product to establish the removal of certain defined contaminants. Validation studies showed that ---------- are reproducibly removed to acceptable levels in the final bulk drug product. Although additional validation studies showed that ---------- are reproducibly removed to low levels, these impurities are monitored. Assays of the drug substance and drug product have been validated for accuracy, precision and reproducibility. ---------- conformance lots have been submitted to CBER for testing and have been shown to meet the testing requirements.

Various steps in the purification process, e.g. solvent detergent treatment and column chromatography, have been validated for their ability to remove viruses that may not have been detected in the production cells. The ------- model and relevant viruses used in Baxter's studies include: ----------. These ------- viruses cover the range of physico-chemical properties of viruses expected in this type of manufacturing process. Overall, the purification process has been shown to reduce these viruses by a factor of at least --- logs. No testing, or purification validation, has been carried out for bovine spongiform encephalopathy (BSE). Neither bovine components nor bovine serum albumin is used in the cell culture manufacturing process. Thus, the possibility of introducing BSE into the ADVATE rAHF-PFM manufacturing process is considered to be negligible.

C. Stability

The stability of the drug substance has been investigated in -------- batches for up to ----------. Data to date indicate that the drug substance is stable for ---------- when maintained at ---------C.

The stability of the drug product has been investigated in a minimum of ----- lots at each of the respective potencies (------- lots of the 250-IU, ----- lots of the 500-IU, ---------- lots of the l000-IU, and ---- lots of the l500-IU potencies). ---------- months of real time data have been collected on ------ lots of the 500-IU and ------ lots of the 1000-IU potencies. A minimum of ---- months of real time stability data has been collected on all drug product lots under evaluation. The real time data, along with data from accelerated studies at ---------- and at elevated temperatures (----------C) indicate that the drug product is stable for 18 months when maintained at 2 - 8°C. ADVATE rAHF-PFM may be stored at room temperature (22° - 28°C) for a period of up to six (6) months until the expiration date. Studies of the reconstituted drug product indicated that it is stable for ---------- at room temperature. Nevertheless, the reconstituted product should be administered within three (3) hours to assure aseptic use.

D. Labeling

The product labeling consists of a physician package insert (full prescribing information), a patient package insert, vial labels, and unit cartons. The package insert (full prescribing information), container (vial), and package (unit carton) labels are in compliance with 21 CFR 201 Subparts A and B and 21 CFR §610.60, §610.61 and §610.62. The trade name, ADVATE, is not known to be in conflict with or easily confused with the trademark of any other licensed pharmaceutical product.

E. Establishment

Pre-license establishment inspections of the Baxter Healthcare Corporation ---------- ---------- production facility in Neuchâtel, Switzerland, and the Baxter Healthcare Corporation final drug product production facility in ---------- were conducted on ---------- A biennial establishment inspection of the Baxter Healthcare Corporation final drug product production facility in ---------- --------- was also conducted on ----------. A pre-approval inspection of the Baxter Healthcare Corporation labeling and packaging facility in ---------- ---------- was waived. A biennial establishment inspection of this facility was conducted on ----------. An FDA Form 483 was issued at each location for each inspection; the firm responded to all observations and their corrective actions were found to be adequate and complete. All three establishments were found to be in compliance with current good manufacturing practice standards. A copy of the inspection reports, the inspectional closeout memoranda, and the inspection waiver for ---------- facility are on file.

F. Environmental Assessment

Baxter Healthcare Corporation filed a request for a categorical exclusion under 21 CFR 25.31(c) from an Environmental Assessment. This request was found to be justifiable.

IV. Pharmacology and Toxicology

The safety, toxicity, efficacy, and absorption, distribution, metabolism, and elimination (ADME) of ADVATE rAHF-PFM have been tested in animals.

A. Pharmacology

The hemostatic efficacy of ADVATE rAHF-PFM was compared with that of RECOMBINATE rAHF in Factor VIII-deficient mice. For this study, mice received either 150 IU/kg body weight RECOMBINATE rAHF or ADVATE rAHF-PFM. Thirty minutes post-dosing, each tail was transected and blood samples were collected every 4 minutes over a period of 20 minutes. The cumulative blood loss was calculated by sequentially adding the blood volumes of each collected sample. An evaluation of the mean blood loss versus time demonstrated that hemostatic efficacy of ADVATE rAHF-PFM and RECOMBINATE rAHF were comparable.

B. Pharmacokinetics

Pharmacokinetic parameters of ADVATE rAHF-PFM were compared with those of the currently licensed product, RECOMBINATE rAHF, in ---------- rats. Animals were anticoagulated, and then treated with ADVATE rAHF-PFM (400 IU/kg) or RECOMBINATE rAHF (400 IU/kg). Blood samples were drawn pre- and post-infusion for determination of Factor VIII pharmacokinetics. Area under the plasma concentration vs. time curve (AUC) values were 5900 ± 1503 mIU/mL/h and 6748 ± 1653 mIU/mL/h for RECOMBINATE rAHF and ADVATE rAHF-PFM, respectively. Half-lives were 1.54 ± 0.33 h and 1.55 ± 0.47 h for RECOMBINATE rAHF and ADVATE rAHF-PFM, respectively. Mean retention times were 1.85 ± 1.08 h and 2.44 ± 1.20 h and mean clearance rates were 71.86 ± 17.69 mL/h/kg and 63.22 ± 18.99 mL/h/kg for RECOMBINATE rAHF and ADVATE rAHF-PFM, respectively. No statistically significant differences were observed in the pharmacokinetics of the two concentrates.

V. Medical

A. Overview of Clinical Data

The Chinese Hamster Ovary (CHO) cell lines for production of ADVATE rAHF-PFM and anti-Factor VIII (FVIII) monoclonal antibody (MAb) have been adapted to culture media that do not contain any components of human or animal origin. The final product is formulated and stabilized without added excipients of human or animal origin. "This process *virtually* [emphasis added] eliminates any risk of transmission of human blood-borne viruses or other adventitious agents that could, in theory, be introduced by the use of animal-derived proteins." It is noted, however, that the final container product may contain traces of murine MAb from the immunoaffinity purification step, as well as CHO protein. Approximately 2% of subjects in the clinical trials of ADVATE rAHF-PFM demonstrated a rise in antibodies to either CHO or murine protein, but in no case had manifest clinical allergic correlates. The product manufacturing includes solvent detergent viral inactivation. The commercial scale material used in the "continuation study" is produced by a manufacturing method at ------ the pilot scale that was used for the pivotal clinical trial. The manufacturing facilities of the bulk drug substance for pilot and commercial scale ADVATE rAHF-PFM are different (Orth, Austria and Neuchâtel, Switzerland, respectively).

Baxter has conducted a 3-part pivotal trial (**#069901**) in subjects previously-treated (PTPs) with Factor VIII (AHF), to evaluate pharmacokinetics (PK), immunogenicity, hemostatic efficacy, and safety. The first part of study 069901 was a PK comparison of pilot-scale rAHF-PFM to the sponsor's marketed RECOMBINATE rAHF, but was to be conducted in only half the trial subjects (randomly selected). The 2nd part of study 069901 involved multi-dose (≥ 75 exposure days) safety and neoantigenicity determination in all trial subjects. The 3rd part was conducted in those who did not participate in the initial PK comparison, and was a PK comparison of pilot scale rAHF-PFM to commercial-scale rAHF-PFM. Following conclusion of participation in that pivotal trial, subjects were offered the opportunity to participate in a continuation neoantigenicity/safety protocol (#**060102**) using commercial-scale material manufactured at different manufacturing facilities compared to that used for the pilot-scale clinical trial material (CTM). The sponsor, in compliance with prior agreement made with the Center for Biologics Evaluation and Research (CBER), submitted interim study data on 27 PTP subjects having had ≥ 50 exposure days from the commercial-scale CTM study. Baxter also submitted data from interim analyses of 2 supportive trials in (1) surgery (protocol #**069902**, data on 10 of 25 planned subjects submitted) using either bolus or continuous infusion and (2) a pediatric PTP study in a planned total of 50 children < 5 years of age (#**060101** – PTPs). The interim data from the surgical and pediatric studies primarily involved use of pilot-scale material. ---------
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The primary and secondary endpoints of pivotal study #069901 were as follows:

PRIMARY

1. To compare AUC for test product and currently-licensed RECOMBINATE rAHF to establish bioequivalence.

2. To compare AUC for test product made at pilot vs. commercial scales to determine bioequivalence.

SECONDARY

1. Area under "moment curve," plasma half-life, clearance, mean residence time, volume of distribution at steady state, C_{max}, adjusted (for baseline FVIII:C level) recovery to compare test product to RECOMBINATE rAHF.

2. Area under "moment curve," plasma half-life, clearance, mean residence time, volume of distribution at steady state, C_{max}, adjusted recovery to compare test product made at pilot vs. commercial scales.

3. To assess the risk of inhibitor (neutralizing anti-factor VIII antibodies) development after a minimum of 75 exposure days to CTM i.e., rAHF-PFM. The sponsor estimated that 80 subjects provide sufficient sample size to rule out a > 6.7 % or greater incidence of inhibitor formation with 95% confidence, should a single subject develop an inhibitor. If the outcome mirrors the experience with licensed RECOMBINATE rAHF and no inhibitors are detected, the sponsor shall have ruled out an inhibitor incidence at or below 5 %.

4. To assess the number of exposure days of test product prior to inhibitor development.

5. To evaluate hemostatic efficacy of CTM in the management of acute bleeding events, as measured on a scale of none, fair, good, or excellent. To assess the mean number of infusions required to achieve adequate hemostasis for all bleeding episodes. To assess the mean number of new bleeds per month – both total and those secondary to trauma.

6. To assess short- and medium-term safety of ADVATE rAHF-PFM.

Although CBER does not apply the term "bioequivalence" to biological products, all of the pivotal study objectives were met and the primary and secondary outcome variables were achieved satisfactorily. In particular only 1 inhibitor (low level < 5.0 BU) was identified among the trial participants who received pilot-scale material. Thus, the upper bound of the 95% one-sided CI for high-level inhibitor development is 5.4%. No inhibitors were seen among 27 subjects who had ≥ 50 exposure days in the continuation study, in which subjects received commercial-scale material, in which most subjects from the pivotal trial participated.

The following [subjective] hemostatic efficacy rating scale was used by the subject for home infusion, or by the investigator for hospital-based infusions:

1. **Excellent**: abrupt pain relief and/or unequivocal improvement in objective signs of bleeding (e.g., swelling, tenderness, decreased range of motion (ROM) in the case of musculo-skeletal (MS) hemorrhage) within approximately 8 hours after a single infusion.

2. **Good**: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion but possibly requiring more than one infusion for complete resolution.

3. **Fair**: probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requiring more than one infusion.

4. **None**: no improvement, or condition worsens.

A total of 510 new bleeding episodes were treated with the pilot-scale test article under this protocol as of the original BLA submission. Of these, 439 (86%) were rated excellent or good in global response to treatment, 61 (12%) were rated fair, 1 (0.2%) was rated as having no response, and for 9 (2%) the response was listed as "unknown". A total of 411 (81%) of new bleeding episodes were treated with only a single infusion, 62 (12%) required 2 infusions, 15 (3%) required 3 infusions, and 22 (4%) required 4 or more infusions of test article. Spontaneous new bleeding episodes occurred in 162 (32%) instances; antecedent trauma was present for 228 bleeds (45%), and [surprisingly] the data as to whether bleeds were spontaneous or traumatic were missing for 120 (24%) of episodes. The mean ± SD number of bleeding episodes over the trial observation period was 6.1 ± 8.2 bleeds per subject. T**he overall rate of bleeding episodes during [despite] routine prophylaxis with the product was 0.52 (0 - 3.88) bleeds per subject per month**. The sponsor inferred in a *post-hoc* analysis that there is an inverse relationship between compliance with the recommended routine prophylactic regimen and bleeding frequency/rate.

The interim analyses of the surgical study (n = 10) and of the pediatric PTP study data were supportive of the efficacy and safety of the product. An interim analysis of inhibitor development in 15 of 50 planned pediatric subjects < 6 years of age

who had at least 50 prior exposure days to Factor VIII at study entry was conducted. No subject completed 50 exposure days to ADVATE rAHF-PFM. Ten of the 15 enrolled subjects completed at least 10 exposure days to ADVATE rAHF-PFM or 120 total days on study; among this subset, there were no inhibitors. A total of 54 subjects ≤ 16 years of age have been treated across all studies of ADVATE rAHF-PFM to date. Interim pharmacokinetic data for 34 subjects (per-protocol analysis population) ≤16 years of age were obtained from a combined dataset comprising subjects 10 to 16 years of age treated on the Phase 2/3 pivotal study and subjects enrolled and treated on the ongoing study of pediatric previously treated subjects < 6 years of age. Among these, 0 were neonates (birth to < 1 month of age), 2 were infants (1 month to < 2 years of age), 15 were children (2 to 12 years of age), and 17 were adolescents (12 to = 16 years of age). Pharmacokinetic parameters were not significantly different for the different pediatric age categories. The following pharmacokinetic parameters were determined for the 34 subjects = 16 years of age in the per-protocol analysis population: The mean ± SD plasma half-life was 11.21 ± 2.92 hours (range: 8.31- 24.7 hours). The mean AUC_{0-48h} was 1363 ± 440 IU·h/dL. The mean values for C_{max} and adjusted recovery were 109 ±23 IU/dL and 2.17 ± 0.44 IU/dL / IU/kg, respectively.

Adverse reactions were examined in an integrated safety analysis of all completed and ongoing studies submitted 28 January 2003, and in additional analyses requested by CBER to conform to FDA's classification of pediatric subjects based on age. Results are presented for a total of 96 subjects > 16 years of age and 54 subjects ≦ 16 years of age who received at least one infusion of ADVATE rAHF-PFM.

For subjects > 16 years of age, the mean ± SD and median (range) values for time on study per subject were 319 ± 213 days and 403 days (1 to 654); the mean ± SD and median (range) exposure days to ADVATE rAHF-PFM per subject were 130 ± 84 days and 140 days (1 to 289); and the mean ± SD and median (interquartile range) IU/kg per infusion were 32.0 ± 8.27 IU/kg and 30.7 IU/kg (27.8 to 33.8).

For subjects ≤ 16 years of age, the mean ± SD and median (range) values for time on study per subject were 321 ± 210 days and 428 days (1 to 651); the mean ± SD and median (range) exposure days to ADVATE rAHF-PFM per subject were 138 ± 93 days and 181 days (1 to 284); and the mean ± SD and median (interquartile range) IU/kg per infusion were 36.5 ± 11.7 IU/kg and 33.4 IU/kg (29.7 to 40.4).

Across all clinical studies, a total of 1304 adverse events were reported among 128 of the 150 subjects who received at least 1 infusion of ADVATE rAHF-PFM. Of the 1304 adverse events, 696 were reported among 85 subjects > 16 years of age and 608 were reported among 43 subjects 16 years of age. Adverse events (product-related and unrelated) by preferred term reported by at least 10% of subjects comprised pharyngolaryngeal pain (22 events in 17 subjects), fall (25 events in 19 subjects), pyrexia (37 events in 25 subjects), nasopharyngitis (32 events in 22 subjects), accidents (62 events in 26 subjects), limb injury (195 events

in 52 subjects), arthralgia (74 events in 35 subjects), headache (138 events in 44 subjects), and cough (37 events in 23 subjects).

Eighteen of the 1304 adverse events were deemed serious; none were considered by the clinical investigator to be related to the study medication. There were no deaths. Among the 1286 non-serious adverse events, only 28 in 12 subjects were judged by the investigator to be related to the study drug. Severity ratings among the 28 events were mild in 8 cases, moderate in 16 cases, and severe in 4 cases.

The mild or moderate events considered at least possibly product-related comprised dysgeusia, pruritus, dizziness, headaches, catheter-related infection, rigors, hot flushes, diarrhea, lower limb edema, sweating, nausea, upper abdominal pain, chest pain, prolonged bleeding after postoperative drain removal, decreased hematocrit, joint swelling, and dyspnea.

The severe related adverse experiences comprised pyrexia, headache, hematoma, and decreased coagulation Factor VIII levels. The unexpected decreased coagulation Factor VIII levels occurred in one subject during continuous infusion of ADVATE rAHF-PFM following surgery. The investigator considered that this subject experienced normal hemostatic efficacy from use of the test product.

The sponsor has demonstrated substantial evidence of safety and efficacy for ADVATE rAHF-PFM for its intended use in the prevention (surgical) and treatment of bleeding in moderately-severe and severe hemophilia A. [

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The sponsor has accepted the phase IV commitments outlined below. Included is provision for FDA to consider the possible adequacy of data from an interim-analysis of continuous infusion and intermittent bolus infusion in surgical prophylaxis from the ongoing PTP study, such interim analysis to be submitted by the end of 2003, as a possible alternative to performing a new, randomized study comparing intermittent bolus infusion to continuous infusion. The sponsor has committed to performing the proposed randomized trial of the use of ADVATE rAHF-PFM in surgical prophylaxis comparing intermittent bolus infusion to continuous infusion should CBER find that the data regarding continuous infusion from the to-be-submitted interim analysis of the surgical study is inadequate to evaluate the risks and benefits of administration of the product by continuous infusion, in comparison to the traditional mode of administration by intermittent bolus infusion.

B. Detailed Summary of Clinical Data

Food and Drug Administration investigators conducted Good Clinical Practice inspections under the Bioresearch Monitoring Program of three selected clinical investigator sites with regard to the ADVATE rAHF-PFM pivotal studies. The sites audited included the Comprehensive Bleeding Disorder Center in Peoria, IL, USA on November 4 to 20, 2002; the Indiana Hemophilia and Thrombosis Center in Indianapolis, IN 46260, USA on November 18 to 22, 2002; and the University Hospital of Wales, Haemophilia Centre and Haemostasis in Cardiff, UK on January 20 to 24, 2003. In addition, FDA investigators also conducted inspections of two central laboratories, which included the ----------, Baxter Healthcare Corporation in ---------- to November 8, 2002; and the ----------

The inspection of the Indiana Hemophilia and Thrombosis Center, the University of Wales's Haemophilia Centre and Haemostasis Unit and the ---------- revealed no significant deviation from applicable federal regulations governing the conduct of clinical studies involving investigational new drugs. The two remaining audited sites (the Comprehensive Bleeding Disorder Center and the ----------) each received a Form FDA 483.

Correspondence addressing concerns raised by the inspections were issued to each site. In light of the inspectional findings at one central laboratory, CBER requested Baxter to undertake and provide the results of a site audit of the laboratory and identify all instance of FVIII:C sample re-analysis, provide supplementary analyses of all protocol-required PK parameters, evaluate the impact of the results of the supplementary analysis on the primary and secondary analysis conclusions. CBER concluded that the re-analyses do not change any conclusions involving the primary and secondary endpoint data.

Written response to the Form FDA 483 received from the ---------- and the Comprehensive Bleeding Disorder Center adequately addressed the inspectional observations at these two sites. Thus, the clinical investigations of ADVATE rAHF-PFM are considered to have complied with current Good Clinical Practices.

A). Pharmacokinetics

Pharmacokinetics of ADVATE rAHF-PFM in Previously Treated Subjects [3] 10 Years of Age

Comparison of ADVATE rAHF-PFM (Orth) and RECOMBINATE rAHF

Pharmacokinetic parameters of ADVATE rAHF-PFM were examined in a pivotal Phase 2/3 study of ADVATE rAHF-PFM in previously treated subjects ≥ 10 years

of age. Fifty-six (56) subjects were randomized to a pharmacokinetic comparison of rAHF-PFM produced at pilot-scale in a facility in Orth, Austria and RECOMBINATE rAHF. Complete blinding was potentially hindered by the fact that licensed RECOMBINATE rAHF was reconstituted to a volume of 10 mL/500 IU nominal potency, while rAHF-PFM was reconstituted to a volume of 5 mL/500 IU nominal potency. The initial washout prior to PK study infusion was 72 hours. Pre-infusion FVIII:C level was required to be ≤ 5% (5 IU/mL), as documented by prior measurement ≥ 72 hours following the most recent treatment. The product was to be infused over ≤ 5 minutes (maximum infusion rate 10 mL/min), "using a nominal potency of 500 IU/vial for both [PK] study infusions [in part I]." Sampling times of FVIII:C in part I of the pivotal PK trial were at 0, 15 and 30 min, 1, 3, 6, 9, 24, 28, 32, and 48 hours post-infusion.

Thirty (30) subjects were eligible for the per-protocol analysis. In this analysis, mean (range) values for AUC_{0-48h} were 1515 (970-2205) IU·h/dL and 1533 (876 - 2642) IU·h/dL for RECOMBINATE rAHF and rAHF-PFM (Orth), respectively. Mean (range) adjusted recoveries were 2.55 (1.47 - 3.89) IU/dL per IU/kg and 2.40 (1.54 - 3.88) IU/dL per IU/kg for RECOMBINATE rAHF and rAHF-PFM (Orth), respectively. Mean (range) half-lives were 11.4 (7.9 - 18.1) h and 12.0 (6.7 - 24.7) h for RECOMBINATE rAHF and rAHF-PFM (Orth), respectively. For the pharmacokinetic parameters AUC_{0-48h} and *in vivo* recovery, 90% confidence intervals for the ratios of the mean values for the RECOMBINATE rAHF and rAHF-PFM were within the pre-established limits of 0.80 and 1.25.

Supplementary analyses of the pharmacokinetic parameters described above were conducted based on (1) the initial assay result, (2) the last assay result, and (3) the arithmetic mean of all assay results for all samples for which multiple factor assay results were obtained. In the per-protocol analysis, parameters calculated using the first (F), last (L), and arithmetic mean (M) results were as follows. For AUC_{0-48h}, mean (± SD) values were 1545 ± 395.0 IU·h/dL (F), 1516 ± 367.0 IU·h/dL (L), and 1530 ± 380.0 IU·h/dL (M) for RECOMBINATE rAHF and 1534 ± 436.0 IU·h/dL (F), 1533 ± 435.0 IU·h/dL (L), and 1534 ± 436.0 (M) for ADVATE rAHF-PFM (Orth). For adjusted recoveries mean (± SD) were 2.63 ± 0.57 IU/dL per IU/kg (F), and 2.56 ± 0.54 IU/dL per IU/kg (L), and 2.59 ± 0.52 IU/dL per IU/kg (M) for RECOMBINATE rAHF and 2.42 ± 0.52 IU/dL per IU/kg (F), and 2.40 ± 0.49 IU/dL per IU/kg (L), and 2.41 ± 0.50 IU/dL per IU/kg (M) for rAHF-PFM (Orth). For half-life, mean (± SD) were 11.13 ± 2.49 h (F), 11.39 ± 2.66 h (L), and 11.24 ± 2.53 h (M) for RECOMBINATE rAHF and 11.98 ± 4.28 h (F), 11.98 ± 4.28 h (L), 11.98 ± 4.28 h (M) for rAHF-PFM (Orth). Ninety percent (90%) confidence intervals for the ratios of the mean values of AUC_{0-48h} and adjusted recovery for the rAHF-PFM (Orth) and RECOMBINATE rAHF using the first, last, and arithmetic means were within the pre-established limits of 0.80 and 1.25.

Comparison of rAHF-PFM (Orth) and ADVATE rAHF-PFM (Neuchâtel)

Fifty-five (55) subjects were randomized to a pharmacokinetic comparison of rAHF-PFM produced at pilot-scale in Orth (control article) and ADVATE rAHF-PFM produced at commercial-scale in a facility in Neuchâtel, Switzerland. Thirty-seven (37) subjects met the criteria for the per-protocol analysis. Mean (range) values of $AUC_{0\text{-}48h}$ were 1544 (856 - 2216) IU·h/dL and 1494 (767 - 2392) IU·h/dL for rAHF-PFM (Orth) and ADVATE rAHF-PFM (Neuchâtel), respectively. Mean (range) adjusted recoveries were 2.55 (1.73 - 4.05) IU/dL per IU/kg and 2.46 (1.71 - 3.41) IU/dL per IU/kg for rAHF-PFM (Orth) and ADVATE rAHF-PFM (Neuchâtel), respectively. Mean (range) half-lives were 11.6 (7.6 - 15.0) h and 11.7 (8.1 - 17.3) h for rAHF-PFM (Orth) and ADVATE rAHF-PFM (Neuchâtel), respectively. Ninety percent (90%) confidence intervals for the ratios of the mean values of $AUC_{0\text{-}48h}$ and adjusted recovery for the rAHF-PFM (Orth) and ADVATE rAHF-PFM (Neuchâtel) were within the pre-established limits of 0.80 and 1.25.

Supplementary analyses of the pharmacokinetic parameters described above were conducted based on (1) the initial assay result, (2) the last assay result, and (3) the arithmetic mean of all assay results for all samples for which multiple factor assay results were obtained. In the per-protocol analysis, parameters calculated using the first (F), last (L), and arithmetic mean (M) results were as follows. For $AUC_{0\text{-}48h}$, mean (± SD) values were 1509 ± 415.0 IU·h/dL (F), 1544 ± 407.0 IU·h/dL (L), and 1511 ± 416.0 IU·h/dL (M) for rAHF-PFM (Orth) and 1469 ± 407.0 IU·h/dL (F), 1494 ± 400.0 IU·h/dL (L), and 1466 ± 409.0 (M) for ADVATE rAHF-PFM (Neuchâtel). For adjusted recovery, mean (± SD) values were 2.68 ± 0.75 IU/dL per IU/kg (F), 2.55 ± 0.52 IU/dL per IU/kg (L), and 2.61 ± 0.63 IU/dL per IU/kg (M) for rAHF-PFM (Orth) and 2.46 ± 0.52 IU/dL per IU/kg (F), and 2.46 ± 0.45 IU/dL per IU/kg (L), and 2.43 ± 0.50 IU/dL per IU/kg (M) for ADVATE rAHF-PFM (Neuchâtel). For half-life, mean (± SD) values were 11.81 ± 1.94 h (F), 11.60 ± 2.01 h (L), and 11.72 ± 1.86 h (M) for rAHF-PFM (Orth) and 11.63 ± 2.13 h (F), 11.72 ± 2.15 h (L), and 11.63 ± 2.13 h (M) for ADVATE rAHF-PFM (Neuchâtel). Ninety percent (90%) confidence intervals for the ratios of the mean values of $AUC_{0\text{-}48h}$ and adjusted recovery for ADVATE rAHF-PFM (Neuchâtel) and rAHF-PFM (Orth) using the first, last, and arithmetic means were within the pre-established limits of 0.80 and 1.25.

Comparison of Pharmacokinetics of ADVATE rAHF-PFM Before and After at Least 75 Exposure Days

Potential changes in the pharmacokinetics of ADVATE rAHF-PFM from the onset of treatment versus after at least 75 exposure days within the same cohort of subjects were investigated in the context of a Phase 2/3 continuation study involving subjects who completed treatment on the Phase 2/3 pivotal study. This comparison utilized data for rAHF-PFM (Orth) obtained at the onset of treatment on the pivotal Phase 2/3 study with data for ADVATE rAHF-PFM (Neuchâtel) obtained in the continuation study. A total of 13 of 34 eligible subjects were included in an interim per-protocol analysis. Among 13 patients who met the criteria for the per-protocol analysis, the mean ± SD values for $AUC_{0\text{-}48h}$ were 1313

± 403 IU·h/dL at the onset of treatment and 1262 ± 497 IU·h/dL after at least 75 exposure days. The mean ± SD values for adjusted recovery were 2.21 ± 0.43 IU/dL per IU/kg at the onset of treatment and 2.20 ± 0.51 IU/dL per IU/kg after at least 75 exposure days. The mean ± SD values for terminal phase half-life were 11.10 ± 2.72 h at the onset of treatment and 10.89 ± 1.37 h after at least 75 exposure days. Ninety-five percent (95%) confidence intervals calculated for the ratios of the mean values for $AUC_{0\text{-}48h}$ and in vivo recovery before and after at least 75 exposure days indicated no evidence of a difference in the pharmacokinetics of ADVATE rAHF-PFM at the two time points.

Supplementary analyses of the pharmacokinetic parameters described above were conducted based on (1) the initial assay result, (2) the last assay result, and (3) the arithmetic mean of all assay results for all samples for which multiple factor assay results were obtained. Pharmacokinetic parameters calculated before and after at least 75 exposure days to ADVATE rAHF-PFM for the cohort of 13 subjects described above were recalculated using the first (F), last (L), and arithmetic mean (M) values for factor VIII. For $AUC_{0\text{-}48h}$, 95% confidence intervals for the difference in the natural log-transformed mean values at the onset of treatment and after at least 75 exposure days based on the first, last, and arithmetic mean values for factor VIII were -0.035 to 0.148, -0.035 to 0.144, and –0.035 to 0.146, respectively. For adjusted recovery, 95% confidence intervals for the difference in the natural log-transformed mean values at the onset of treatment and after at least 75 exposure days based on the first, last, and arithmetic mean values for factor VIII were -0.067 to 0.130, -0.071 to 0.099, and –0.067 to 0.113, respectively. All sets of confidence intervals included 0, which demonstrated no evidence of a difference in the pharmacokinetic parameters after long-term exposure to ADVATE rAHF-PFM.

Pharmacokinetics in Pediatric Subjects < 16 Years of Age

The pharmacokinetics of ADVATE rAHF-PFM (Neuchâtel) have been examined in an interim analysis of subjects treated on an ongoing study of young (< 6 years of age) pediatric previously treated subjects with moderately severe to severe hemophilia A. Additional data were obtained for subjects 10 to 16 years of age treated in the Phase 2/3 pivotal study and subjects > 5 years of age treated on the ongoing Phase 2/3 surgery study.

Preliminary pharmacokinetic data for subjects < 6 years of age are available from an interim analysis of 14 subjects (intent-to-treat analysis population) or 11 subjects (per-protocol analysis population) in the ongoing study of pediatric previously treated subjects. In the intent-to-treat analysis, the mean ± SD value for terminal phase half-life was 10.00 ± 1.79 h (range: 7.41-13.87). The mean ± SD value for $AUC_{0\text{-}48h}$ was 1395 ± 483 IU·h/dL. The mean ± SD value adjusted recovery was 1.96 ± 0.49 IU/dL per IU/kg. In the per-protocol analysis, the mean terminal phase half-life was 10.48 ± 1.60 h (range: 8.31 - 13.87). The mean ± SD value for $AUC_{0\text{-}48h}$ was 1521 ± 467 IU·h/dL, and the mean ± SD value adjusted recovery was 2.06 ± 0.51 IU/dL per IU/kg. A per-protocol analysis of pediatric subjects ≤ 16 years of

age using the combined data for subjects 10 to 16 years of age treated on the Phase 2/3 pivotal study and the interim data for subjects < 6 years of age treated on the ongoing study of pediatric previously treated subjects. Among these, 0 were neonates (birth to < 1 month of age), 2 were infants (1 month to < 2 years of age), 15 were children (2 to 12 years of age), and 17 were adolescents (12 to ≤ 16 years of age).

Pharmacokinetic parameters were not significantly different for these different age categories. For the combined group of subjects ≤ 16 years of age, the mean (± SD) plasma half-life was 11.21 ± 2.92 hours (range: 8.31- 24.7 hours), the mean $AUC_{0\text{-}48h}$ was 1363 ± 440 IU·h/dL, and the mean values for C_{max} and adjusted recovery were 109 ± 23 IU/dL and 2.17 ± 0.44 IU/dL per IU/kg, respectively.

In conclusion, the pharmacokinetic results described herein are consistent with those observed in association with other licensed plasma-derived and recombinant Factor VIII concentrates, including RECOMBINATE rAHF. To the extent that one accepts pharmacokinetic data as a surrogate for efficacy in hemophilia A, the PK findings imply that ADVATE rAHF-PFM is likely to be effective in children and adults with moderately-severe to severe hemophilia A.

B). Efficacy

Hemostatic Efficacy of ADVATE rAHF-PFM in Previously Treated Subjects

Hemostatic efficacy of rAHF-PFM (Orth) was determined in Baxter's pivotal Phase 2/3 study, during which subjects were treated with rAHF-PFM on a routine prophylactic regimen of 25 - 40 IU/kg administered 3 to 4 times per week for a minimum of 75 exposure days. ADVATE rAHF-PFM was also administered for the treatment of all new bleeding episodes (either spontaneous or trauma-related) that occurred during the treatment period. A total of 510 bleeding episodes occurred in 83 subjects; 20 episodes involved more than one site. Of the 510 bleeding episodes, 439 (86%) were rated as having an excellent/good response to treatment, 61 (12%) were rated as having a fair response, 1 (0%) was rated as having no response, and for 9 (2%) the response was listed as "unknown." Overall, 411 (81%) of bleeding episodes required treatment with 1 infusion of ADVATE rAHF-PFM, 62 (12%) required 2 infusions, 15 (3%) required 3 infusions, and 22 (4%) required ≥ 4 infusions. The overall mean weight-adjusted dose for all 510 bleeding episodes was 52.15 ± 67.06 IU/kg. Per infusion, the mean and median doses were 38.1 IU/kg and 32.9 IU/kg, respectively for all etiologies of bleeding episodes.

The overall rate of new bleeding episodes was 0.52 episodes/subject/month (range: 0 to 3.88). In a post-hoc analysis, the overall rate of bleeding was correlated inversely with the degree of compliance with the prescribed prophylactic regimen. Good compliance was defined as treatment at the protocol-specified dose (≥ 25 IU/kg/infusion) for at least 80% of infusions and at or above the protocol-specified

infusion frequency (3 to 4 times per week) for at least 80% of the weeks on study. Notably, the mean rate of all new bleeding episodes was more than two-fold higher for the 37 subjects who were less compliant (0.82 episodes/subject/month) than for the 70 subjects who received infusions at doses and frequencies at or above those specified in the protocol (0.36 episodes/subject/month). This effect appeared to be generally consistent across age groups and all bleeding etiologies, but was most prominent in the subset of episodes that occurred secondary to trauma. Subjects who had good compliance with the prescribed prophylactic regimen had, on average, a 50% reduction in the rate of trauma-related bleeding episodes compared with their less compliant counterparts.

The **Phase 2/3 continuation study** involved subjects previously treated in the pivotal Phase 2/3 study and provided additional efficacy data on ADVATE rAHF-PFM (Neuchâtel). An interim analysis of efficacy was conducted for 27 of 82 enrolled subjects who self-administered ADVATE rAHF-PFM produced in Neuchâtel on a routine prophylactic regimen during a minimum period of 50 exposure days to ADVATE rAHF-PFM. As in the pivotal Phase 2/3 study, new bleeding episodes were treated with ADVATE rAHF-PFM and the outcome of treatment was rated as excellent, good, fair, or none, based on the quality of hemostasis achieved. A total of 51 new bleeding episodes occurred in 13 of the 27 subjects receiving with ADVATE rAHF-PFM. By etiology, 53% of these bleeding events resulted from trauma and 27% occurred spontaneously; the other 20% had an undetermined etiology. The response to treatment with ADVATE rAHF-PFM for the majority (63%) of all new bleeding episodes was rated as excellent or good. Interestingly, this percentage is statistically significantly lower ($p < 0.05$) than the percentage of bleeding episodes whose response to pilot-scale ADVATE was rated excellent or good. However, 86% of the bleeding episodes in the interim analysis of the continuation study resolved with only 1 infusion and an additional 6% were resolved by a second infusion. Thus, 92% of all bleeding episodes required 1 or 2 infusions of study product, which was similar to the results obtained in the pivotal trial for pilot-scale rAHF-PFM. Of 27 analyzed subjects who have had a minimum of 50 exposure days to the commercial-scale formulation, none tested positive for an inhibitor.

Hemostatic Efficacy for Perioperative Management of Patients Undergoing Surgical Procedures

An interim analysis of the hemostatic efficacy of ADVATE rAHF-PFM during the perioperative management of subjects undergoing surgical procedures was conducted for 10 of 25 planned subjects. Ten subjects underwent 10 surgical procedures while receiving ADVATE rAHF-PFM. Eight subjects received the test product by intermittent bolus infusion and 2 subjects received a combination of continuous and intermittent bolus infusion. Nine of the 10 subjects completed the study. Six of the surgical procedures were classified as major, and 4 were minor. Of the 6 major surgeries, 5 were for orthopedic complications of hemophilia. For all 10 surgical procedures, intra- and post-operative assessments were reported as

excellent/good by the responsible surgeon and the investigator. Actual blood loss for 9 of 10 subjects was within the predicted average and maximal range of blood loss expected for patients with normal hemostasis undergoing the same type of surgical procedure. The remaining one subject experienced blood loss approximately 30% higher (2900 mL) than the expected maximal blood loss (2000 mL). This subject underwent a total hip replacement and the investigator rated overall hemostatic efficacy as good. None of the subjects developed postoperative hematomas. Only one subject experienced bleeding at the site of the operation but this occurred approximately 1 month after the surgery and was judged to respond to ADVATE rAHF-PFM treatment. None of the 10 analyzed surgery subjects tested positive for Factor VIII inhibitors at study termination.

C). Safety

Adverse reactions were examined among a total of 96 subjects > 16 years of age and 54 subjects ≤ 16 years of age who received at least one infusion of ADVATE rAHF-PFM. For subjects > 16 years of age, the mean ± SD and median (range) values for time on study per subject were 319 ± 213 days and 403 days (1 to 654); the mean ± SD and median (range) exposure days to ADVATE rAHF-PFM per subject were 130 ± 84 days and 140 days (1 to 289); and the mean ± SD and median (interquartile range) IU/kg per infusion were 32.0 ± 8.27 IU/kg and 30.7 IU/kg (27.8 to 33.8).

For subjects ≤ 16 years of age, the mean ± SD and median (range) values for time on study per subject were 321 ± 210 days and 428 days (1 to 651); the mean ± SD and median (range) exposure days to ADVATE rAHF-PFM per subject were 138 ± 93 days and 181 days (1 to 284); and the mean ± SD and median (interquartile range) IU/kg per infusion were 36.5 ± 11.7 IU/kg and 33.4 IU/kg (29.7 to 40.4).

Across all clinical studies, a total of 1304 adverse events were reported among 128 of the 150 subjects who received at least 1 infusion of ADVATE rAHF-PFM. Of the 1304 adverse events, 696 were reported among 85 subjects > 16 years of age and 608 were reported among 43 subjects 16 years of age. Adverse events (product-related and unrelated) by preferred term reported by at least 10% of subjects comprised pharyngolaryngeal pain (22 events in 17 subjects), fall (25 events in 19 subjects), pyrexia (37 events in 25 subjects), nasopharyngitis (32 events in 22 subjects), accidents (62 events in 26 subjects), limb injury (195 events in 52 subjects), arthralgia (74 events in 35 subjects), headache (138 events in 44 subjects), and cough (37 events in 23 subjects).

Eighteen of the 1304 adverse events were deemed serious; none were considered by the clinical investigator to be related to the study medication. There were no deaths.

Among the 1286 non-serious adverse events (AEs), only 28 in 12 subjects were judged by the investigator to be related to the study drug. Severity ratings among

the 28 events were mild in 8 cases, moderate in 16 cases, and severe in 4 cases. The finding of a 2-fold excess of moderate AEs over mild AEs, among the subset of AEs considered at least possibly related to administration of study drug, raises the possibility that some mild AEs (such as headache) possibly related to administration may have been misclassified as unrelated. In most clinical trials, mild AEs are more common than AEs classified moderate in intensity.

The mild or moderate events considered at least possibly product-related comprised dysgeusia, pruritus, dizziness, headaches, catheter-related infection, rigors, hot flushes, diarrhea, lower limb edema, sweating, nausea, upper abdominal pain, chest pain, prolonged bleeding after postoperative drain removal, decreased hematocrit, joint swelling, and dyspnea. The case of moderate dyspnea occurred at least 1 day following the infusion.

The severe related adverse experiences comprised pyrexia, headache, hematoma, and decreased coagulation Factor VIII levels. The unexpected decreased coagulation Factor VIII levels occurred in one subject during continuous infusion of ADVATE rAHF-PFM following surgery (postoperative Days 10 - 14). Hemostasis was reportedly maintained at all times during this period and both plasma Factor VIII levels and clearance rates returned to appropriate levels by postoperative Day 15. Factor VIII inhibitor assays performed after completion of continuous infusion and at study termination were negative in this subject. The case of severe pyrexia began more than 1 hour after completion of the infusion but on the day of infusion. The case of moderate dyspnea occurred at least 1 day following the infusion.

There were no discernable temporal trends in the occurrence of any particular type of adverse experience. The majority (n=1003; 77%) of adverse experiences occurred at least one calendar day after an infusion, whereas a minority (n= 87) occurred during an infusion (57 events) or ≤ 1 hour after the infusion (30 events); most (72 of 87) of these were judged to be unrelated to the study drug.

Factor VIII inhibitor testing was performed throughout all studies in the rAHF-PFM clinical program. The subjects in the pivotal trial of pilot-scale material had blood samples tested for inhibitors every 15 ± 2 days for a total of at least 75 exposure days. Factor VIII inhibitors were to be classified as positive inhibitors, low titer inhibitors, high titer inhibitors, and transient inhibitors according to the following definitions:

- Low titer inhibitor: 1.0 B.U. ≤ titer ≤ 5.0 B.U. OR 0.6 B.U. ≤ titer ≤ 5.0 B.U (by the Nijmegen modification).
- High titer inhibitor: titer > 5.0 B.U.
- Transient inhibitor: titer ≤ 5 B.U., which is not detectable in two consecutive inhibitor assays and at study termination
- All: any low titer, high titer, or transient inhibitor

Among 136 treated subjects ≥ 10 years of age, all of whom had ≥150 exposure days to Factor VIII products at study entry, 102 had at least 75 exposure days to ADVATE rAHF-PFM on study. None of these subjects were reported to have developed an inhibitor. One study subject who had < 50 exposure days to ADVATE rAHF-PFM while on study developed an inhibitor. This subject manifested a low titer inhibitor (2.0 BU/mL by the Bethesda assay) after 26 ADVATE rAHF-PFM exposure days. Eight weeks later, the inhibitor was no longer detectable, and *in vivo* recovery was normal at 1 and 3 hours after infusion of RECOMBINATE rAHF. For the group comprising all subjects with at least 75 exposure days to ADVATE rAHF-PFM and the single subject who developed an inhibitor, the 95% confidence interval (Poisson distribution) for the risk of developing an inhibitor to Factor VIII was 0.02% to 5.4%.

An interim analysis of inhibitor development in 15 of 50 planned pediatric subjects < 6 years of age who had at least 50 prior exposure days to Factor VIII at study entry was conducted. No subject completed 50 exposure days to ADVATE rAHF-PFM. Ten of the 15 enrolled subjects completed at least 10 exposure days to ADVATE rAHF-PFM or 120 total days on study; among this subset, there were no inhibitors.

Assessments of development of antibodies to trace contaminants (CHO protein, murine IgG, and human recombinant VWF) in the ADVATE rAHF-PFM final drug product showed no safety concerns related to the presence of anti-CHO, anti-murine IgG, or anti-VWF antibodies. In addition, examination of changes in laboratory parameters and vital signs indicated no evidence of toxicity of the study product in any of the studies.

In conclusion, a cumulative integrated safety analysis of data from 4 clinical studies in 2 non-overlapping cohorts of subjects has demonstrated that ADVATE rAHF-PFM is safe and reasonably well-tolerated in children and adults with moderately severe or severe hemophilia A in a wide variety of clinical settings. The observed incidence of inhibitor formation over 75+ exposure days in previously-treated subjects > age 10 is acceptable, as is the upper bound of the 95% confidence interval, based on the Poisson distribution (5.4%). The data on inhibitor formation in pediatric PTPs under age 6 is very limited, but will be expanded in a phase IV continuation of the pediatric PTP study. Experience with the product in children between the ages of 6 and 10 is lacking. However, based on the similar preliminary safety and efficacy findings in children < 6 years of age and the experience in subjects > 10 years of age in the pivotal trial, no surprises in the safety or efficacy of the product in children between the ages of 6 and 10 are anticipated.

D). Studies in Previously Untreated Patients

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VI. Post-Marketing Studies and Commitments

The sponsor has committed to the following:

1. To submit a protocol within 6 months of the date of product approval for the conduct of an adequately-powered randomized study of the product in routine prophylaxis which compares 2 different dosing regimens/frequencies. To initiate the study within 6 months of the date that FDA conveys to the sponsor its agreement with the proposed study design, and, once the study has been completed, to file the final study report of the study to both the Investigational New Drug Application (IND) and BLA under 21 CFR 601.70 in a timely manner.

2. To submit a protocol within 12 months of the date of product approval for the conduct of a randomized study of the product in surgery, comparing the safety and efficacy of the product administered by intermittent bolus infusion versus continuous infusion. To initiate the study within 6 months of the date that FDA conveys to Baxter its agreement with the proposed study design, and, once the study has been completed, to file the final study report of the study to both the IND and BLA under 21 CFR 601.70 in a timely manner. Depending on CBER's judgment of the adequacy of the data regarding the use of rAHF-PFM administered by continuous versus intermittent bolus infusion, which is to be submitted to CBER by the end of 2003 in the form of an interim report for ongoing clinical study # 069902, CBER reserves the right to consider that the submission of such data from study # 069902 may obviate the need and phase IV requirement to conduct the randomized study described in the first part of this paragraph.

3. To complete and report to the IND and BLA in a timely fashion the results of several ongoing and planned clinical studies specified in the approval letter.

4. ----------

5. ----------

6. To submit to CBER a complete summary of all ADVATE rAHF-PFM-PFM lots produced during each quarter-year. To submit to CBER samples and protocols for every 5th lot of each dosage strength manufactured.

7. To commit that those lots of rAHF-PFM final drug product produced before September 10, 2002 will not be distributed to the US market.

VII. Package Insert

A copy of the package insert is attached.