
Memorandum

Date January 28, 1997

From Director, Office of Orphan Products Development (HF-35)

Subject Clinical Superiority of Genetics' Institute coagulation factor IX product, BeneFix™

To OOPD Application

A Biological License Application (BLA) has been submitted by Genetics Institute for BeneFix™ Coagulation Factor IX (recombinant) for the treatment and prevention of bleeding in hemophilia B patients. BeneFix™ is the third coagulation factor IX to receive orphan drug designation for the treatment of hemophilia B. The other two products are plasma-derived Coagulation Factor IX (human): AlphaNine® (Alpha Therapeutic, approved December 31, 1990) and Mononine® (Centeon, then Armour Pharmaceutical, approved August 20, 1992). Mononine® was approved despite the orphan exclusivity of AlphaNine® because at that time the manufacturing process for Mononine® gave greater assurance of safety with respect to human blood-borne viruses, especially hepatitis C. Currently, both products are manufactured by methods that are effective in reducing the risk of transmitting human viruses; however, these risks have not been totally eliminated. Furthermore, the potential risk of transmitting the causative agent of Creutzfeldt-Jakob disease (CJD) remains uncertain, but has led to the recall of large quantities of plasma derivatives.

BeneFix™ is the recombinant analog of the two plasma derived factor IX products. It has the same principal molecular structural features as AlphaNine® and Mononine® and is intended for the same use. Hence, BeneFix™ would be considered the same drug as AlphaNine® and Mononine® unless it can be shown to be clinically superior to the previously approved products. Since Genetics Institute does not claim nor would the information in the BLA support that BeneFix™ is more effective than the previously approved products, the claim to clinical superiority rests on the greater safety of BeneFix™.

By virtue of its source and manufacturing methods, BeneFix™ is inherently less likely to transmit human blood-borne viruses and other infectious agents, and is also less likely to transmit animal-derived zoonotic agents than is AlphaNine® and Mononine®. The greater safety of BeneFix™ with respect to its reduced risk of disease transmission is attributable to two factors:

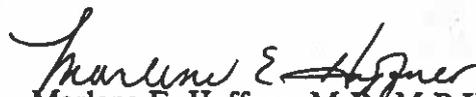
1. BeneFix™ is a recombinant product produced in CHO-derived cells *in vitro*, rather than from human plasma. Moreover, no human-derived protein is added during the production,

isolation or formulation of BeneFix™. Thus the risk of transmitting infectious agents that may be present in human plasma has been eliminated.

2. No animal derivative is added or used during the manufacture of BeneFix™. In particular, the affinity chromatography methods used to produce Mononine® (immobilized murine Mab) and AlphaNine® (immobilized porcine heparin) are not employed in the manufacture of BeneFix™. Thus the risk of transmitting animal derived zoonotic agents has been reduced.

No direct comparative studies between BeneFix™ and either AlphaNine® or Mononine® have been conducted to confirm the reduced risk of viral transmission presumed to exist for BeneFix™. Such studies would not be practical given the small number of hemophilia B patients and the infrequency at which most blood-borne viruses are transmitted by the currently licensed products. However, it is known from epidemiological studies that human parvovirus B19 and, much less frequently, hepatitis A can be transmitted by plasma-derived coagulation factor IX preparations. These viruses do not exist in the source material from which BeneFix™ is produced, nor in any component utilized during its manufacture. Therefore, it is reasonable to conclude that, barring a breakdown in cGMPs, the risk associated with this and other human blood-borne viruses has been eliminated in BeneFix™.

The Office of Orphan Product Development (OOPD) concurs with CBER's decision that the increased safety of BeneFix™ can be intuitively derived and does not need to be demonstrated in comparative trials. We also concur that the effects of viral and prion transmission are so catastrophic that even a very low frequency of occurrence represents a significant risk to patients with factor IX deficiency, and any reduction in this risk justifies a finding of greater safety. Like CBER, OOPD is very concerned that products not be deemed different based on trivial findings; however, the elimination of disease transmission represents a very significant benefit to the public health and is an adequate reason to allow a similar product to enter the market.



Marlene E. Haffner, M.D., M.P.H.

Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

Summary of Basis for Approval

Reference Number: 96-1048
Drug Licensed Name: Coagulation Factor IX (Recombinant)
Manufacturer: Genetics Institute, Inc.
Drug Trade Name: BeneFix™

I. Indication for use

BeneFix™, Coagulation Factor IX (Recombinant), is indicated for the control and prevention of hemorrhagic episodes in patients with hemophilia B (congenital factor IX deficiency or Christmas disease). This indication includes the peri-operative management of hemophilia B patients undergoing surgery.

BeneFix™ is not indicated for the treatment of other coagulation factor deficiencies (e.g., factors II, VII and X), nor for the treatment of hemophilia A patients with inhibitors to coagulation factor VIII, nor for the reversal of coumarin-induced anticoagulation. BeneFix™ is also not indicated for the treatment of multiple liver-dependent coagulation factor deficiencies caused by liver disease or dysfunction.

II. Dosage Form, Route of Administration and Recommended Dosage

The BeneFix™ is a sterile, non-pyrogenic, lyophilized powder for injection available in nominal dosage strengths of 1000, 500, and 250 International Units (I.U.) per vial. One International Unit is the amount of factor IX activity present in 1 ml of pooled, normal human plasma. Potency, in I.U., is determined by an *in vitro* one-stage clotting assay, using the World Health Organization International Standard for factor IX concentrates.

After reconstitution of the lyophilized powder with Sterile Water for Injection (USP), the 500 and 1000 I.U. dosage strengths of BeneFix™ comprise approximately 100 I.U./ml, 0.26 M glycine, 1% sucrose, 10 mM L-histidine, and 0.005% polysorbate 80, pH 6.8. The reconstituted 250 I.U. dosage strength of BeneFix™ comprises about one-half these concentrations or approximately 50 I.U./ml, 0.13 M glycine, 0.5% sucrose, 5 mM L-histidine, and 0.0025% polysorbate 80, pH 6.8. The 500 and 1000 I.U. dosage strengths of BeneFix™ are approximately isotonic, whereas the 250 I.U. dosage strength is hypotonic.

The lyophilized formulation contains no preservatives, nor any added animal or human raw materials.

BeneFix™ is administered only by intravenous infusion within 3 hours after reconstitution.

Treatment with BeneFix™, as for all factor IX products, should be initiated under the supervision of a physician.

Clinical studies have shown that the recovery of BeneFix™ is significantly lower (by about 28%) than that of a high purity, plasma-derived factor IX (see below). Empirically, one I.U. of BeneFix™ per kilogram of body weight is expected to increase the circulating

activity of factor IX by 0.8 I.U./dl. The following formula provides a guide to empirical dosage calculations:

Number of factor IX I.U. required	=	Body Weight (in kg)	×	Desired factor IX Increase (%)	×	1.2 I.U./kg
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Alternatively, the estimation of the required dose of BeneFix™ can be based on prior experience with plasma-derived factor IX and titrated upward if necessary to achieve the desired clinical response.

The proper dosage of BeneFix™, as well as the frequency of infusion, can be expected to vary with the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition, age and recovery of factor IX. Dosing guidelines such as given in reference 1 may be useful in estimating appropriate dosage.

For surgical interventions and for life-threatening hemorrhage, precise monitoring of the factor IX replacement therapy using a factor IX activity assay is advised.

III. Manufacturing and Controls

A. Manufacturing

The active ingredient in BeneFix™ is Coagulation Factor IX (Recombinant), a 415-amino acid glycoprotein (approximately 55 kDa) that is produced in Chinese hamster ovary (CHO) cells. The production cells were stably transfected with the gene for the Ala¹⁴⁸ allelic form of plasma-derived factor IX, which by allelic frequency would account for 20% of the factor IX in current products (the remaining 80% having Thr at this position). The production cells were also stably transfected with the gene for the human paired basic amino acid cleaving enzyme (PACE), necessary for the efficient removal of the pro-peptide from the translation product.

The post-translational modifications of the recombinant molecule have been extensively characterized and appear to be generally similar to those of the plasma-derived molecule. Subtle differences have been noted in the complexity of the N-linked carbohydrates, those found in BeneFix™ being a subset of those occurring in the natural product. BeneFix™ is γ-carboxylated on an average of 11.5 residues, whereas 12 residues are normally γ-carboxylated. These minor differences are not known to alter the structure or function of BeneFix™. Of greater significance, the sulfation of Tyr¹⁵⁵ (>90% in plasma derived factor IX vs. ~25% in BeneFix™) and the phosphorylation of Ser¹⁵⁸ (unphosphorylated in BeneFix™) appear to affect the *in vivo* recovery of the recombinant product (see discussion of the pharmacokinetic analysis of BeneFix™ in the clinical summary).

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1. Roberts, H.R. and Eberst, M.E. 1993. Current management of hemophilia B. *Hematol. Oncol. Clin. North Amer.* 7(6): 1269-1280.

A production campaign begins by thawing an ampoule of the production cells, maintained as a Working Cell Bank, expanding the culture in spinner flasks, a bioreactor, and finally the bioreactors in which production takes place in a batch-refeed mode. As many as bioreactors may be utilized in a campaign, which may be inoculated from each other, or from the bioreactor, as validated.

The production cell line has been adapted to suspension cell culture in defined growth medium that is not supplemented by human- or animal-derived proteins. Other than the proteins secreted by the production cell line, the only protein used in the production process for recombinant factor IX is recombinant human insulin (produced in *E. coli*) which is a component of the culture medium. In addition, both the MCB and the WCB have been adapted for growth and cryopreserved (-135°C) in the absence of human or animal protein.

Recombinant factor IX is purified from the culture medium by means of a four-step chromatography process. The purification process also contains a nanofiltration step capable of reducing viral burden. Other than use of the CHO cell line and recombinant human insulin made in *E. coli*, no human or plasma products are used in the manufacture or formulation of BeneFIX™.

The drug substance is manufactured at the Andover, Massachusetts facility of Genetics Institute. Frozen (-80°C) bulk is then shipped to a contract manufacturer for final formulation, sterile filtration, aseptic filling and lyophilization. The contractor also tests the final containers for sterility and particulates, labels and packages the product and ships the released product to distribution centers. All other release testing and quality assurance functions are performed by Genetics Institute.

Final container testing includes potency, specific activity, activated factor IX, SDS-PAGE (purity and identity), SEC-HPLC (purity and protein concentration), sterility, endotoxin, appearance, moisture, solubility, pH and concentrations of the major excipients. The final drug product does not contain other proteins of any kind added as excipients or stabilizers.

B. Validation

The production cell line has been cryopreserved as a Master Cell Bank (MCB), from which a Working Cell Bank (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, fungal or viral contamination.

The manufacturing process for BeneFIX™ has been validated for consistency, robustness, and for removal of impurities. In particular, validation studies and ongoing, periodic revalidation have been accepted in lieu of lot by lot testing of drug substance or final drug product to establish the removal of certain defined

contaminants. These validation studies include removal of host cell proteins, PACE, rhInsulin, methotrexate, and DNA, and have indicated that each of these potential contaminants is reproducibly removed to acceptable levels in the final drug product.

Assays of the drug substance and the final container material have been validated for accuracy, precision and reproducibility. All final container lots have been shown to conform to requirements for identity, purity, potency and sterility according to 21 CFR Part 610. Five conformance lots have been submitted to CBER for testing and have been shown to meet the requirements for potency, residual moisture, and sterility.

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, above. Two of the chromatography columns and the nanofiltration step (molecular weight cutoff 70,000) were evaluated using appropriate model viruses (amphotropic murine leukemia virus; bovine parvovirus, human herpes simplex virus type I, reovirus type 3). Overall, the purification process has been shown to reduce these viruses by a factor of at least 10^{10} .

Summary of Prospective Scale Evaluation of Removal/Inactivation

Virus	Q Sepharose FF	Chelate-EMD-Cu(II)	Viresolve-70	Overall
A-MuLV	6.11 ^a	NA	>5.66	>11.8
BPV	5.42	2.19	4.86	12.5
HSV	4.49	3.92	>5.55	>14.0
Reo-3	5.45	0.15	5.86	11.3 ^b
^a	Log ₁₀ removal value			
^b	Does not include the 0.15 LRV determined for the Chelate-EMD-Cu(II) column step.			

C. Stability Studies

The stability of the drug substance has been investigated in four batches for up to 24 months. Data to date indicate that the drug substance is stable for 24 months when maintained at -80°C and for 6 months when maintained at -20°C.

The stability of the drug product has been investigated in three lots of the 250-I.U. dosage strength, one lot of the 500-I.U. dosage strength, and three lots of the 1000-I.U. dosage strength. Only one lot (1000 I.U.) has been studied under intended storage conditions for a full 24-month period. Data for 18 months have been accumulated for 5 other lots. Coupled with accelerated studies at room temperature and at 40°C, 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 6

months at room temperature. Studies of the reconstituted material have indicated that it is stable for at least 24 hours at room temperature, but nevertheless should be administered within three hours of reconstitution to assure aseptic use.

D. Labeling

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

E. Establishment Inspections

A combined prelicense and biennial establishment inspection of the Andover, MA production facility of Genetics Institute was conducted from November 11 to 15, 1996 by inspectors from OELPS and OBRR, CBER and from BOS-DO. The most recent biennial establishment inspection of the McPherson, Kansas facility of Sanofi Winthrop Pharmaceuticals was conducted from August 19 to 22, 1996 by inspectors from OELPS, CBER and from KAN-DO. Both establishments were found to be in compliance with current good manufacturing practices. Copies of the inspection reports are on file.

F. Environmental Assessment

A report of the impact on the environment is included in the license application.

BeneFix™ produces a hemostatic correction in hemophilia B dogs similar to human pdFIX as exhibited by shortened whole blood clotting time, shortened partial thromboplastin time and correction of secondary bleeding times.

Intravenous doses up to 200 I.U./kg have been administered to dogs and rats without any observed toxicity other than those associated with the development of antibodies. High doses (≥ 500 I.U./kg) of BeneFix™ administered to mice by intraperitoneal injection result in thromboses and consumptive coagulopathy. By comparison with the exposure data and toxicological findings in rats and dogs, the mouse appears to be uniquely susceptible to BeneFix™ and is therefore of uncertain value with respect to human risk assessment.

The thrombogenic potential of BeneFix™ was evaluated in the Wessler stasis model (New Zealand White rabbits). Studies were conducted comparing BeneFix™ with one Coagulation Factor IX Complex (Human) (PCC) and two high purity Coagulation Factor IX (Human) products (pdFIX). The PCC was administered at doses of 15 and 50 I.U./kg and as expected, thrombi were observed at both doses. BeneFix™ was administered at doses of 50, 150, 500 and 1000 I.U./kg and each pdFIX was administered at 1000 I.U./kg. Evidence of thrombosis was seen at the high dose of pdFIX but not at the higher doses of BeneFix™. One animal that had been treated with BeneFix™ at 150 I.U./kg became thrombotic, but because of the lack of a dose response relationship, the latter observation was judged not to be biologically relevant.

No reproductive, developmental or carcinogenicity studies were performed. The mutagenic and clastogenic potential of BeneFix™ was assessed by means of the Ames assay and chromosomal aberration assay with human peripheral blood lymphocytes. Both studies yielded negative results at levels of BeneFix™ estimated to be 60-100 times greater than anticipated in the clinical population.

V. Medical

Inspections of four of the clinical sites were conducted in October 1996. The sites were found to be in compliance with current good clinical practices with regard to the Coagulation Factor IX (Recombinant) studies.

Genetics Institute, Inc. conducted four clinical studies of BeneFix™ safety and efficacy. The first study (C9407-21) was composed of three segments. The first segment, conducted in 11 patients, was a double-masked, crossover pharmacokinetic comparison of BeneFix™ and a high purity Coagulation Factor IX (Human) (pdFIX). After completing the first study segment, all 11 patients administered BeneFix™ as needed for spontaneous bleeding episodes (on-demand therapy) during the second study segment. Of these patients, 10 completed the 12-month visit. A third segment, surgical prophylaxis, was included if any of the 11 patients required surgery during study participation. This study is complete.

The second study (C9408-21) is composed of three segments, the first of which is an open-label, baseline pharmacokinetic evaluation of BeneFix™ followed by replacement therapy with BeneFix™ as appropriate for the individual patient. The second treatment segment allows on-demand therapy identical to that of the second segment of study C9407-21 and routine secondary prophylaxis for the patients who have been on such a regimen for at least 6 months before participating in the study. As in the first study, a third segment provides for surgical prophylaxis if needed. Study C9408-21 is ongoing.

The third study (C9417-21) was a surgical prophylaxis study in which patients with factor IX deficiency were enrolled if they were to undergo elective, major surgical procedures that required factor IX replacement therapy. This study is complete.

The fourth study (C9418-21) is a study of BeneFix™ in previously untreated patients. This study is ongoing.

A safety update was submitted November 1, 1996, reporting results accrued as of August 31, 1996. The data reported in this submission were not included in the evaluation of efficacy. One adverse event was reported to the IND subsequent to the safety update.

A. Pharmacokinetics

The crossover pharmacokinetic evaluation of BeneFix™ and pdFIX was performed at doses of 50 I.U./kg in 11 previously treated patients. The design of this study conformed to the guidelines published by the International Society on Thrombosis and Hemostasis. Both products were well tolerated and corrected the prolonged PTT characteristic of hemophilia B. Elimination half-lives for BeneFix™ and pdFIX were not significantly different (18.1 ± 5.1 hours and 17.7 ± 5.3 hours, respectively). However, the recovery of BeneFix™ was 28% lower than that of pdFIX ($37.8 \pm 14.0\%$ and $52.6 \pm 12.4\%$, respectively; $p=0.0004$). That is, BeneFix™ produced a mean increase in circulating factor IX activity of 0.84 I.U./dl per I.U./kg administered, compared to 1.17 I.U./dl per I.U./kg for pdFIX. These pharmacokinetic parameters were similar in subsequent evaluations at 6 and 12 months. These parameters also did not differ significantly among patients treated with four drug product lots manufactured from several batches of drug substance produced from 2 separate inoculum runs.

B. Previously Treated Patients

The efficacy of BeneFix™ in previously treated patients with moderate or severe hemophilia B was assessed in an open-label phase 1/2 and phase 2/3 study of on-demand, self-administered treatment and peri-operative use of BeneFix™ (C9407-21 and C9408-21). The patients were not stratified according to the severity of the factor IX deficiency, nor was any attempt made to directly compare BeneFix™ with any other product. All endpoints were based on the subjective evaluation (Excellent, Good, Moderate, No Response, Failure) by either the patient or the physician. Routine secondary prophylaxis was also subjectively graded: Excellent, Effective, Inadequate, Failure.

A total of 37 patients have been enrolled in the efficacy portions of C9407-21 and C9408-21, of whom 36 were included in the efficacy analysis. Six lots of BeneFix™ from three separate campaigns were used in this study. No patient reported "failure" of treatment with BeneFix™, however, one patient discontinued participation at the one month follow-up visit because of a lack of response. In 35 of 36 patients who were treated for a bleeding episode, 82% of all bleeding episodes (301/369) required a single infusion of BeneFix™ for resolution and 5.7% (21/369) required three or more infusions. Of the infusions administered, 90% (437/488) were reported as providing excellent or good response. However, data correlating the initial dose administered with the severity of the bleeding episode were not obtained.

For patients treated on a routine secondary prophylaxis regimen 88% of responses (14/16) were rated as "excellent" or "effective" in preventing bleeding. Of 29 "spontaneous" (without concurrent injury) musculoskeletal bleeding episodes in patients on routine secondary prophylaxis, none occurred within 24 hours of an infusion and 7 occurred within 72 hours of an infusion. No data was provided regarding previous prophylactic use of pdFIX (e.g., dosing or effectiveness) or comparing the recoveries (or other pharmacokinetic parameters) of BeneFix™ with pdFIX. The data regarding prophylactic use of BeneFix™ is therefore considered preliminary.

Of the 36 patients enrolled in C9407-21 and C9408-21, 13 patients (on demand and prophylaxis) increased the dose of BeneFix™ administered for subsequent bleeding episodes or ongoing prophylaxis. The results regarding the effectiveness of these dose modifications are preliminary. However, in nine surgical patients, a dose-response relationship between pre-operative bolus BeneFix™ infusion and the first post-infusion activity was established (Pearson $r = 0.74$; $p = 0.0235$), suggesting that the lower *in vivo* recovery can be compensated for by a simple adjustment of the dose of BeneFix™ administered (see page 2).

C. Surgery

As of January 19, 1996, 13 procedures had been performed in 12 patients (6 enrolled in PTP studies [C9407-21 and C9408-21] and 6 exclusively enrolled in the surgical study [C9417-21]).

During the surgical period, 97% of clinical responses were rated as excellent or good by the surgeon or investigator or, when appropriate, by the patient. One patient had moderate response and no response after a single tooth dental extraction which was complicated by significant fibrinolysis. Transfusion of blood products was necessary in only 3 of the 13 procedures (orthotopic liver transplantation and two knee arthroplasties). Estimated blood loss during and after surgery was considered as expected in all cases. No bleeding episodes during the postoperative period were reported.

A total of 1,321,768 units of BeneFix™ were used in these surgical evaluations, including baseline PK evaluations. Total dose administered per procedure during the surgical period ranged from 10,000 I.U. for a dental procedure to 348,000 I.U. for bilateral knee arthroplasties. Preoperative doses ranged from 25 to 155 I.U./kg; doses used in the postoperative period ranged from 30 to 95 I.U./kg. Continuous infusion of BeneFix™ at a rate of 4.3 to 8.6 I.U./kg/hr was used in 3 surgeries. For the other 10 surgeries, a pulse replacement regimen was used.

D. Previously Untreated Patients

Study C9418-21 is a multicenter, open-label phase 1/2 and 2/3 safety and efficacy study of on-demand or prophylactic self-administration and peri-operative use of BeneFix™. Nine patients had been enrolled of whom 3 had received product as of April 19, 1996. Only one patient had received product for treatment of bleeding episodes.

E. Safety

As of August 31, 1996, the clinical studies of BeneFix™ had involved a total of 64 patients (44 previously treated patients, 11 previously untreated patients, and the 9 patients participating in the surgical study) who had received more than 7 million I.U. over a period of 18 months.

A total of 20 previously untreated patients had been enrolled, 11 of whom had been treated with BeneFix™. No adverse reactions related to therapy have been reported after 42 infusions.

Sixty mild adverse reactions definitely, probably, or possibly-related to therapy have been reported for 2458 infusions. These were: nausea (16), discomfort at the IV site (13), altered taste (10), burning sensation in jaw and skull (6), allergic rhinitis (3), lightheadedness (2), headache (2), dizziness (1), chest tightness (1), fever (1), phlebitis/cellulitis at IV site (1), drowsiness (1), dry cough/sneeze (1), rash (1), and a single hive (1). (Data include events reported to the Blood Products Advisory Committee, December 12, 1996.)

A low-level inhibitor was detected in one of 44 patients who had an extensive (>500 exposure days) previous history of treatment with pdFIX without evidence of an inhibitor. Seroconversion in this patient was first observed in the 9-month blood sample by ELISA at 39 exposure days. This patient was able to continue treatment with BeneFix™ with no anamnestic rise in inhibitor or anaphylaxis. By 12/96, the titer of this patient's inhibitor had decreased to undetectable levels. Samples from a second patient reacted weakly and variably in ELISA for antibody to factor IX, but the inhibitor assay remained consistently negative.

Subsequent to the filing of the safety update, Genetics Institute reported preliminary information regarding an acute renal infarct in a 31 year old male enrolled in protocol C9408-21. The patient apparently presented 12 days after the most recent infusion of BeneFix™, at which time he was admitted to hospital. The

patient's workup was inconclusive as to the cause of the infarction, and the investigator judged that the event was unlikely to be related to the drug.

F. Post-Marketing (Phase IV) Studies

Genetics Institute has committed to continuing the following trials until completion during the post-marketing period:

C9408-21 Safety and Efficacy of Coagulation Factor IX (Recombinant) in Previously Treated Patients with Moderate or Severe Hemophilia B.

All patients currently enrolled in this study will continue in the study for a period of 2 years.

C9418-21 Study of the Safety and Efficacy of Coagulation Factor IX (Recombinant) in Previously Untreated Patients with Severe or Moderately Severe Hemophilia B

Approximately 30 patients with severe or moderately severe hemophilia B will be enrolled, at least 15 of whom will be severe hemophiliacs. All patients will be followed for at least 2 years and then up to 100 exposure days or 5 years, whichever is sooner.

VI. Blood Products Advisory Committee

On December 12, 1996, the Blood Products Advisory Committee considered the clinical data submitted in support of the license application for BeneFix™. The committee voted eight yes, five no, with one abstention that the safety data are adequate to support the approval of BeneFix™. In a subsequent vote, the committee voted unanimously for approval of the license application for BeneFix™ subject to continued surveillance for: i) major thrombotic events; ii) other adverse events; iii) inhibitor development; and iv) use in previously untreated patients.

The committee also voted unanimously that the recommended dosing of BeneFix™ be adjusted to account for the lower in vivo recovery of BeneFix™ as compared with pdFIX.

VII. Orphan Drug Considerations

BeneFix™ was designated an orphan drug by the Office of Orphan Products Development on October 3, 1994 (application #94-822). BeneFix™ is the third coagulation factor IX product to receive orphan drug designation for the treatment of hemophilia B. The other two products are plasma-derived Coagulation Factors IX (Human): AlphaNine® (Alpha Therapeutic, approved December 31, 1990) and Mononine® (Centeon, then Armour Pharmaceutical, approved August 20, 1992). Currently, both plasma-derived products are manufactured by methods that are effective in reducing the risk of transmitting human viruses, however these risks have not been totally eliminated. Furthermore, the potential risk of transmitting the causative agent of

Creutzfeldt-Jakob disease (CJD) remains uncertain, but has led to the recall of large quantities of plasma derivatives.

BeneFix™ is the recombinant analog of the two plasma derived factor IX products. It has the same principal molecular structural features as AlphaNine® and Mononine® and is intended for the same use. Hence, BeneFix™ would be considered the same drug as AlphaNine® and Mononine® unless it can be shown to be clinically superior to the previously approved products. Genetics Institute claims the clinical superiority of BeneFix™ because of its greater safety compared to the plasma-derived products.

By virtue of its source and manufacturing methods, BeneFix™ is inherently less likely to transmit human blood-borne viruses and other infectious agents, and is also less likely to transmit animal-derived zoonotic agents than is AlphaNine® or Mononine®. The greater safety of BeneFix™ with respect to its reduced risk of disease transmission is attributable to two factors:

1. BeneFix™ is a recombinant product produced in CHO-derived cells *in vitro*, rather than from human plasma. Moreover, no human-derived protein is added during the production, isolation or formulation of BeneFix™. Thus the risk of transmitting infectious agents that may be present in human plasma has been eliminated.
2. No animal derived protein is added or used during the manufacture of BeneFix™. In particular, the affinity chromatography methods used to produce Mononine® (immobilized murine MAb) and AlphaNine® (immobilized porcine heparin), are not employed in the manufacture of BeneFix™. Thus the risk of transmitting animal derived zoonotic agents has been reduced.

No direct comparative studies between BeneFix™ and either AlphaNine® or Mononine® have been conducted to confirm the reduced risk of viral transmission presumed to exist for BeneFix™. Such studies would not be practical given the small number of hemophilia B patients and the infrequency at which most blood-borne viruses are transmitted by the currently licensed products. However, it is known from epidemiological studies that human parvovirus B19 and, much less frequently, hepatitis A can be transmitted by plasma-derived coagulation factor IX preparations. These viruses do not exist in the source material from which BeneFix™ is produced, nor in any component utilized during its manufacture. Therefore, it is reasonable to conclude that, barring a breakdown of cGMPs, the risk associated with these and other human blood-borne viruses has been eliminated in BeneFix™.

Thus, a significant therapeutic advantage of BeneFix™ (greater safety with respect to transmitting human viruses) over and above that provided by the approved orphan drugs, AlphaNine® and Mononine®, has been shown. In addition, BeneFix™ is otherwise licensable and no countervailing risks have been shown to be associated with BeneFix™. Therefore, BeneFix™ is clinically superior within the meaning of 21 CFR 316.3(b)(3) to

either AlphaNine® or Mononine®, and may be licensed despite the orphan exclusivity of the latter two products.

VIII. Package Insert

A copy of the approved package insert is attached.

Summary Basis for Approval: 96-1048
Coagulation Factor IX (Recombinant) BeneFIX™
Genetics Institute, Inc.

 5/20/97

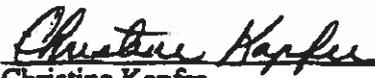
Thomas J. Lynch, Ph.D. Date
HFM-340

 2/5/97

Mark J. Weinstein, Ph.D. Date
HFM-340

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Andrew Chang, Ph.D. Date
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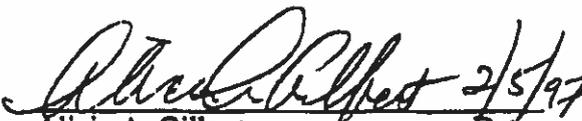
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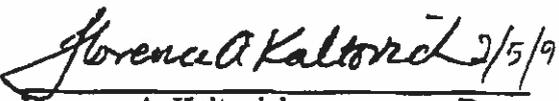
Jaroslav G. Vostal, M.D., Ph.D. Date
HFM-335

 2/5/97

Laura L. Wood Date
HFM-340

 2/5/97

Alicia A. Gilbert Date
HFM-207

 2/5/97

Florence A. Kaltovich Date
HFM-207

Paul M. Aebersold, Ph.D. Date
HFM-380

 MD 2/10/97

Toby A. Silverman, M.D. Date
HFM-380



Jenna M. Weber Date
HFM-380

Cornelius J. Lynch, Ph.D. Date
HFM-215

Jose J. Tavaréz Pagan Date
HFM-650

Martin D. Green, Ph.D. Date
HFM-579

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

**Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857**

April 11, 1994

Genetics Institute, Inc.
Attention: Frederick T. Gates, Ph.D.
Director, Regulatory Affairs
87 CambridgePark Drive
Cambridge, MA 02140

Dear Dr. Gates:

We are pleased to acknowledge receipt of your application for orphan drug designation submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the following:

Name of Drug: coagulation factor IX (recombinant)

Indication: Treatment of hemophilia B.

Date of Application: April 7, 1994

Date of Receipt: April 8, 1994

Our Reference Number:

We will correspond with you further after we have had the opportunity to review the application. Please note that your drug or biological product will not be eligible for designation if you have filed a new drug application (NDA) or product license application (PLA) for this indication. Please refer to our reference number in all future communications with this office.

If you have any questions, please call me at (301) 443-4718.

Sincerely yours,


Peter L. Vaccari, R.Ph.
Senior Regulatory Management Officer

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(301) 443-4903

May 11, 1994

Genetics Institute, Inc.
Attention: Frederick T. Gates, Ph.D.
Director, Regulatory Affairs
87 Cambridge Drive
Cambridge, MA 02140

Dear Dr. Gates:

Reference is made to your orphan drug application of April 7, 1994 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of coagulation Factor IX, recombinant (rhFIX) as an orphan drug (

We have completed the review of this application and request that additional information be submitted summarizing the status, as well as any results, of all nonclinical studies for rhFIX. The information submitted to support the scientific rationale for the use of rhFIX in the treatment of hemophilia B is mostly dedicated to discussing the superiority of rhFIX over currently available blood-derived Factor IX products. Although this information suggests that a recombinant product offers significant advantages over a blood-derived product, the application does not provide the nonclinical data required under 21 CFR 316.20(b)(4). Partial data was provided about the manufacturing and testing process of the CHO line, as well as the half-life of rhFIX in dogs, but it is not clear if this nonclinical information was obtained in your own studies or elsewhere because it is not referenced. Please clarify and provide copies of appropriate references used in support of any new submissions.

Further review of this application is being held in abeyance pending the receipt of the above requested information. A written response to this letter must be received within 90 days from the date of this communication or the file will be considered inactive and withdrawn. Following 90 days, further requests for designation of the same product for the same indication must be made in the form of a new designation application. Information contained in this file may be cross-referenced in support of a new designation request.

Your cooperation is appreciated.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

October 3, 1994

Genetics Institute, Inc.
Attention: Frederick T. Gates, Ph.D.
Director, Regulatory Affairs
87 Cambridge Drive
Cambridge, MA 02140

Dear Dr. Gates:

Reference is made to your orphan drug application of April 7, 1994 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of coagulation Factor IX (recombinant) as an orphan drug. We also refer to your amendments dated July 15 and September 13, 1994.

We have completed the review of this application, as amended, and have determined that coagulation Factor IX (recombinant) qualifies for orphan designation for the treatment of hemophilia B. Please note that it is coagulation Factor IX (recombinant) and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if coagulation Factor IX (recombinant) were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of coagulation Factor IX (recombinant) as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Ms. Erica McNeilly at (301) 443-4718.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

March 25, 1996

Genetics Institute
Attention: John C. Petricciani, M.D.
Vice President, Regulatory Affairs
87 Cambridge Park Drive
Cambridge, MA 02140

Dear Dr. Petricciani:

This is in response to your January 31, 1996 request for a letter from our office regarding PLA filing issues and whether the orphan exclusivity of AlphaNine and Mononine would prevent the Agency from accepting a PLA filing for coagulation factor IX, recombinant (rFIX).

When our office considered designating rFIX as an orphan product, we determined that Genetics Institute had submitted a medically plausible rationale for the potential clinical superiority (safer or more efficacious) of the drug and that the orphan exclusivity already held by AlphaNine and Mononine would not interfere with the designation of rFIX as an orphan drug.

Accordingly, the orphan exclusivity of AlphaNine and Mononine should not prevent the Agency from accepting Genetic Institute's PLA for filing. In addition, rFIX would be eligible for licensing as a commercial product in the United States if the information in the PLA support a claim of greater safety than AlphaNine or Mononine. On the basis of the manufacturing scheme for rFIX containing no human- or animal-derived proteins, rFIX should be inherently safer than plasma-derived products in that there is no potential for contaminants with plasma-derived pathogens.

If you have any other questions or concerns, please feel free to contact our office at (301) 827-3666.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
RADM, USPHS
Director, Office of Orphan Products Development

cc:

Genetics Institute, Inc.

87 CambridgePark Drive
Cambridge, Massachusetts 02140
Telephone (617) 876-1170
Telefax (617) 876-0388

One Burt Road
Andover, Massachusetts 018
Telephone (508) 475-9214
Telefax (508) 475-0085

GENETICS  INSTITUTE

RECEIVED

JAN 13 1997

Office of Orphan
Products Development

Coagulation Factor IX (Recombinant) [rFIX]
Orphan Drug Application
]
Exercise of Orphan Drug Exclusivity

January 8, 1997

Marlene Haffner, M.D., M.P.H.
Office of Orphan Products Development
(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

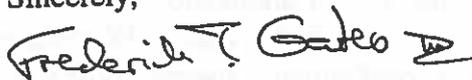
*Noted
PW
1/14/97*

Dear Dr. Haffner:

By letter dated October 3, 1994, Genetics Institute, Inc. received orphan drug designation for Coagulation Factor IX (Recombinant) [rFIX]. The designation letter also indicated that prior to receipt of marketing approval for rFIX, Genetics Institute should submit written notification to you of Genetics Institute's intention to exercise orphan drug exclusivity. On August 29, 1996, Genetics Institute submitted a Biologics License Application for rFIX, and on December 12, 1996, the Blood Products Advisory Committee recommended approval of the product. Therefore, on behalf of Genetics Institute, we hereby notify the Office of Orphan Products Development of our intention to exercise orphan drug exclusivity for rFIX. This notification should facilitate recognition by the FDA of the exclusive approval of rFIX, in accordance with 21 CFR 316 Subpart D.

Please call me at (617) 498-8623, or Tim Ahern, Ph.D, Regulatory Affairs Associate, at (617) 498-8777, if you have any questions or require additional information.

Sincerely,



Frederick T. Gates, Ph.D.
Director, Regulatory Affairs

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are confidential business information or trade secrets of Genetics Institute, Inc., or its licensors and are exempt from disclosure under the Freedom of Information Act (5 USC 552), as set forth in 21 CFR 20.

Review of Request for Orphan Designation

FILE COPY

Designation Number:

Date Received by FDA:	April 8, 1994
Date Received by Reviewer:	April 8, 1994
Date Review Completed:	April 29, 1994
Date Amendment Received:	July 18, 1994
Date Additional Information Received:	September 16, 1994
Date Review Completed:	September 20, 1994

Product: Trade Name: has not been established
Generic Name: coagulation Factor IX (recombinant), rhFIX

Sponsor

Genetics Institute, Incorporated
87 CambridgePark Drive
Cambridge, MA 02140
(617) 876-1170

Contact Person:

Frederick T. Gates, Ph.D.
Director, Regulatory Affairs

Regulatory Status:

RhFIX is currently under development at Genetics Institute.
e)

Indication:

Treatment of hemophilia B.

Conclusions and Recommendations from April 29 Review:

The sponsor has presented satisfactory evidence that the population of patients with hemophilia B in the United States will be clearly less than 200,000, and is approximately 6,000.

Most of the information in the rationale portion of the application discusses the superiority of rhFIX over currently available blood-derived Factor IX products. Although this evidence clearly suggests that a recombinant product offers significant advantages over a blood-derived product, the application does not supply enough data to indicate that rhFIX is anything more than a concept. The sponsor states in the application that an IND will be submitted to FDA in December 1994, so clinical information is not expected, but preclinical information should have been provided. The sponsor does give some limited information about the manufacturing and testing process

of the CHO line, as well as the half-life of rhFIX in the dog, but it is not clear if this nonclinical information was obtained in the sponsor's own studies or elsewhere because this information is not referenced. The only preclinical reference submitted in the application discusses the first purification of Factor IX in CHO cells in 1986.

Data summarizing the status, as well as any results, of all preclinical studies for rhFIX should be submitted.

Sponsor's July 18 Response :

The sponsor provided a summary of their rhFIX preclinical studies, which were performed with product manufactured in their Andover facility. Three studies were discussed; the 28-day rat pharmacology study, 28-day dog pharmacology study, and single-dose dog pharmacokinetic (PK) study of rhFIX versus Mononine™. The first two studies describe the antigenicity of rhFIX in the rat and dog. The last study found the two pharmacokinetic profiles of the two proteins to be similar, except that the area under the curve (AUC) value for Mononine™ was 25% higher. This difference is thought to be due to the lower specific activity of Mononine™ in comparison to rhFIX. The sponsor indicates that "on the basis of these preliminary studies, the efficacy of rhFIX is presently being assessed in hemophilia B dogs."

Evaluation of July 18 Response:

The sponsor has provided a summary of their completed preclinical data, performed using rhFIX manufactured in their own facility. This data does indicate that the sponsor has a product, but the completed studies are preclinical safety studies which do not provide any evidence of efficacy. The sponsor indicates that an efficacy study of rhFIX in dogs with hemophilia B are currently ongoing, but no information about this preclinical efficacy study is provided.

The sponsor was contacted September 1 and asked to submit the results of the preclinical study of rhFIX in the hemophilia B dog model.

Sponsor's September 15 Response :

The results of a study of rhFIX in three hemophilia B dogs were provided by the sponsor. The effect of rhFIX on clotting parameters in the hemophilia B dogs are the following:

<u>parameter</u>	<u>hemophilia dog</u>		<u>normal dogs</u>
	<u>before treatment</u>	<u>after treatment</u>	<u>no treatment</u>
whole blood clotting time	53 ± 10.6 min	10.3 ± 1.0 min	7.5 ± 1.5 min
secondary bleeding time	> 15 min	2.6 ± 0.5 min	3.5 ± 2.5 min
partial thromboplastin time	125 ± 25 sec	60.5 ± 15 sec	37.5 ± 1.5 sec

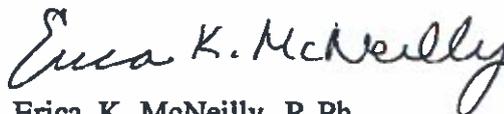
The PK values reported for rhFIX was comparable to those obtained with human-derived factor IX in normal beagle dogs. The sponsor indicates that rhFIX can effectively restore normal hemostasis in dogs with hemophilia B.

Evaluation of September 1 Response:

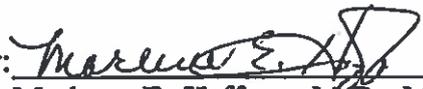
The sponsor summarizes that the these preclinical results indicate that rhFIX can effectively restore normal hemostasis in dogs with hemophilia B and that pharmacokinetic values reported for rhFIX was comparable to those obtained with human-derived factor IX in normal beagle dogs. Although these are preclinical efficacy results, the data does provide satisfactory scientific rationale for the use of rhFIX in the treatment of hemophilia B.

Recommendation:

It is recommended that coagulation Factor IX (recombinant) (rhFIX) be designated an orphan product for the treatment of hemophilia B as required by Section 526 of the Orphan Drug Act.



Erica K. McNeilly, R.Ph.
Reviewing Pharmacist

Concur: 
Marlene E. Haffner, M.D., M.P.H.

Date: 27 September '94

CC:
HF-35/OP File
HF-35/Chron
HF-35/EKMcNeilly 9/20/94 review-2.822

Review of Request for Orphan Designation

FILE COPY

Designation Number:

Date Received by FDA: April 8, 1994
Date Received by Reviewer: April 8, 1994
Date Review Completed: April 29, 1994

Product:

Trade Name: has not been established
Generic Name: coagulation Factor IX (recombinant), rhFIX

Sponsor :

Genetics Institute, Incorporated
87 CambridgePark Drive
Cambridge, MA 02140
(617) 876-1170

Contact Person:

Frederick T. Gates, Ph.D.
Director, Regulatory Affairs

Regulatory Status:

RhFIX is currently under development at Genetics Institute.

Indication:

Treatment of hemophilia B.

Disease Background Information:

Hemophilia is a sex-linked disorder of males. It is characterized by excessive bleeding and a prolongation of blood clotting time. There are three major types of hemophilia: hemophilia A, hemophilia B, and hemophilia C. Hemophilia B, the topic of this application, is also known by its synonym Christmas disease, and is characterized by insufficient or abnormal synthesis of Factor IX.

Activated Factor IX, in the presence of activated Factor VIII, is required for activation of Factor X. Activated Factor X converts prothrombin to thrombin, which in turn catalyzes the cleavage of fibrinogen to fibrin, resulting in the formation of a fibrin clot. Clinical symptoms of hemophilia B depend on the amount of active Factor IX produced by the patient. Those with mild factor IX deficiency may only hemorrhage after trauma

or surgery. In severe cases, hemorrhaging can occur spontaneously, producing orthopedic deformities, organ dysfunction, or death¹. About 50% of patients with hemophilia B have a mild course with only occasional bleeding, but 20% of patients have severe disease that requires regular prophylactic Factor IX replacement therapy.

The symptoms of hemophilia B symptoms are currently treated with ice packs to decrease swelling and discomfort and replacement therapy. Frozen fresh plasma may be used in instances of mild bleeding. For moderate to severe hemorrhaging, commercially prepared factor IX is used.

Population Estimate:

References submitted by the sponsor estimate the population with hemophilia B to range between a minimum of 3,900 to a maximum of 5,200^{2,3}. The highest incidence of hemophilia B in any country is 2.3 per 100,000 in Ireland⁴. Given the current United States population of 260 million, the sponsor indicates that this incidence figure would yield a potential maximum prevalence of 6,000 persons in the United States.

Rationale for Use:

RhFIX exhibits a half-life in dogs comparable to purified plasma-derived factor IX.

The recombinant nature of this factor IX product offers clinical advantages over the approved blood-derived factor IX products, Alphanine™ and Mononine™. Three claims of clinical superiority are:

The use of a recombinant product eliminates the risk of transmitting blood-derived pathogens.

The approved factor IX products are blood derived and carry the risk of transmitting viruses, as well as deleterious nonviral contaminants, to the patient. Examples are contamination of blood-derived coagulation factors with parvovirus⁶, hepatitis A⁷, and the recent case of a recall of blood products due to Hepatitis C infection⁸.

The sponsor does acknowledge the theoretical risk of transmission of viruses associated with the CHO cell culture, but knows of no reports of adverse events resulting from the use of recombinant therapeutic proteins associated with CHO cells that can be attributed to viruses. The CHO cells used in the production of rhFIX have been extensively tested for a large number of viruses and infectious agents and have been demonstrated to be free of any contaminating agent.

A monoclonal antibody is not used in the preparation of this product, so it can be freely used in patients who might be allergic to mouse proteins.

The use of a recombinant product does not involve the risk of thrombosis or disseminated intravascular coagulation (DIC) that is associated with co-administration of other contaminating coagulation factors.

Thrombosis or DIC has been observed to follow administration of blood-derived factor IX concentrates, which contain certain amounts of factors II, VII, and X. Despite the improved purity of Mononine™ relative to other factor IX products, the package insert for Mononine™ still warns of such risks⁹

No information about any preclinical studies performed by the sponsor has been submitted. All of the information in this application about the product rhFIX has been summarized in the first paragraph of this section and only one reference was included to support this data.

Evaluation:

The sponsor has presented satisfactory evidence that the population of patients with hemophilia B in the United States will be clearly less than 200,000, and is approximately 6,000.

Most of the information in the rationale portions of the application discuss the superiority of rhFIX over currently available blood-derived Factor IX products. Although this evidence clearly suggests that a recombinant product offers significant advantages over a blood-derived product, the application does not supply enough data to indicate that rhFIX is anything more than a concept.

so clinical information is not expected, but preclinical information should have been provided. The sponsor does give some limited information about the manufacturing and testing process of the CHO line, as well as the half-life of rhFIX in the dog, but it is not clear if this nonclinical information was obtained in the sponsor's own studies or elsewhere because this information is not referenced. The only preclinical reference submitted in the application discusses the first purification of Factor IX in CHO cells in 1986.

Data summarizing the status, as well as any results, of all preclinical studies for rhFIX should be submitted.

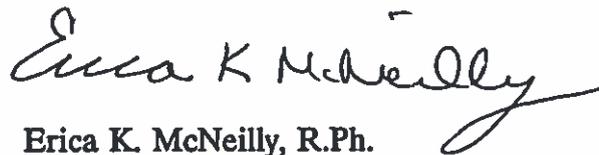
Recommendation:

It is recommended that a deficiency letter be issued to the sponsor:

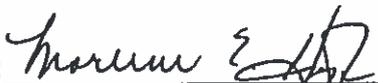
The information submitted to support the rationale portions of this orphan drug designation application are almost solely dedicated to discussing the superiority of rhFIX over currently available blood-derived Factor IX products. Although this evidence clearly suggests that a recombinant product offers significant advantages over a blood-derived product, the application does not supply the nonclinical data as required in

content and format of request for orphan-drug designation (21 CFR § 316.20). You have provided limited information about the manufacturing and testing process of the CHO line, as well as the half-life of rhFIX in the dog, but it is not clear if this nonclinical information was obtained in the your own studies or elsewhere because this information is not referenced. The only nonclinical reference submitted in your the application discusses the first purification of Factor IX in CHO cells in 1986.

Please submit additional information summarizing the status, as well as any results, of all your nonclinical studies for rhFIX.



Erica K. McNeilly, R.Ph.
Reviewing Pharmacist

Concur: 
Marlene E. Haffner, M.D., M.P.H.

Date: 2 May '94

CC:
HF-35/OP File
HF-35/Chron
HF-35/EKMcNeilly 4/29/94

1. Levine PH. Clinical manifestations and therapy of hemophilias A and B. In *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*, 2nd Edition, RW Colman, J Hirsh, VJ Marder and EW Salzman, eds. (J.P. Lippincott Co., Philadelphia), pp. 97-111. 1990.
2. Ibid.
3. Roberts HR and Jones MR. Hemophilia and related conditions - congenital deficiencies of prothrombin (factor II), factor V, and factors VII to XII. In *Hematology*, 4th Edition, WJ Williams, E. Beutler, AJ Erslev, and MA Lichtman, eds. (McGraw-hill, New York). pp 1462-1464. 1990.
4. Etzler, J. Hemophilia statistics: Ireland, Status 1992. IE/ST-2 Hemstat, World Federation of Hemophilia Information Clearing House.
5. Kaufman RJ, Wasley LC, Furie BC, et.al. Expression, purification, and characterization of recombinant gamma-carboxylated Factor IX synthesized in Chinese hamster ovary cells. *J. Biol. Chem* 261:9622-9628. 1986.
6. Azzi A, Ciappi S, Zakvrezeska K, et.al. Human parvovirus B19 infection in hemophiliacs first infused with two high-purity virally attenuated factor VIII concentrates. *Am. J., Hematol.* 39:228-230. 1992.
7. Mannucci PM. Clinical evaluation of viral safety of coagulation factor Viii and IX concentrates. *Vox Sang* 64:197-203. 1993.
8. The Associated Press, Byline: L. Neergarrd. Worldwide recall of blood product because of hepatitis fear. February 25, 1994.
9. Package insert for Mononine™. August, 1992.

Memorandum of Meeting

Date: January 17, 1995

Representing FDA, Office of Orphan Products Development (OPD):

Marlene Haffner, M.D., M.P.H., Director
John J. McCormick, M.D., Medical Reviewer
Erica McNeilly, R.Ph., Consumer Safety Officer

Representing FDA, Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review, Division of Hematology :

Joseph C. Fratantoni, M.D., Director
Mark Weinstein, M.D., Medical Reviewer

Purpose: To discuss exclusivity issues encompassing recombinant factor VIII and recombinant factor IX products.

Background: Recombinant factor IX, sponsored by Genetics Institute, was designated an orphan product on October 3, 1994. There are no recombinant factor IX products on the market, although two sponsors presently market human-derived factor IX. (e

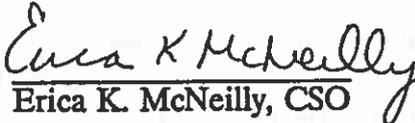
Pharmacia met with representatives from OPD and CBER on November 21, 1994 to discuss filing orphan designation for their recombinant factor VIII product. Currently, Miles and Baxter jointly hold exclusivity for recombinant factor VIII. Pharmacia will have to provide either evidence of clinical superiority or proof that their recombinant factor VIII is a different product to break this exclusivity.

Discussion and Conclusions: The protein structure of Genetics Institute's recombinant factor IX is identical to human derived factor IX. However, the recombinant product will be formulated without the use of any human components so there is no risk of passing any pathogen found in human blood. It appears to both CBER and OPD that Genetic's Institute recombinant factor IX can be considered clinically superior to the presently marketed human-derived factor IX products, provided that equivocal efficacy can be determined between the recombinant and human-derived products.

The presently marketed recombinant factor VIII products are identical to the natural human derived factor VIII. Pharmacia's recombinant factor VIII product contains about half of the

amino acid (AA) sequence of the natural product. Deleting half of the AA sequence does not appear to alter the specific activity of the Pharmacia's product and Pharmacia states that their smaller, different molecule may potentially reduce immunogenicity risk because of fewer sites to produce antibodies. Pharmacia's product is manufactured with human albumin, although no albumin is used in the administration of the product.

It appears to CBER and OPD that Pharmacia's recombinant factor VIII product is potentially different from the currently marketed recombinant factor VIII products because there is a major difference in AA sequence. It also appears to CBER that this major difference in AA sequence is likely to produce a potential significant difference in antigenicity.


Erica K. McNeilly, CSO

cc: GCF-1/J. Cohen /
OP File ;
HF-35/C-----
HF-35/Attendees
HF-35/E. McNeilly reconfac.min dt:1/20/95; ft: 1/24/95
Concurrences: J.McCormick, M.Haffner 1/23/95.



Genetics Institute, Inc.

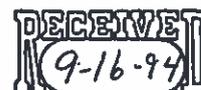
87 CambridgePark Drive
Cambridge, Massachusetts 02140
Telephone (617) 876-1170
Telefax (617) 876-0388

FILE COPY

Recombinant Human Factor IX (rhFIX)
Orphan Drug Application

September 15, 1994

Marlene Haffner, M.D., M.P.H.
Office of Orphan Products Development
(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Haffner:

This letter is a follow-up to our telephone conversation with Erica McNeilly of September 1 concerning Genetics Institute's orphan drug application for recombinant human Coagulation Factor IX (rhFIX). At her request, we are supplying a summary of the results of the preclinical study of rhFIX in the hemophilia B dog model that was recently completed (see attached). This study was performed in collaboration with Dr. Kenneth Brinkhous (University of North Carolina) using rhFIX manufactured by Genetics Institute.

Based on our telephone conversation, we understand that review of the summary provided here should be sufficient to complete the review of our orphan drug application. Please call me at (617) 498-8623, or Maryann Krane, Senior Regulatory Affairs Associate, at (617) 498-8737, if you have any questions.

Sincerely,

A handwritten signature in black ink that reads "Frederick T. Gates, Ph.D." with a stylized flourish at the end.

Frederick T. Gates, Ph.D.
Director, Regulatory Affairs

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are confidential business information or trade secrets of Genetics Institute, Inc., or its licensors and are exempt from disclosure under the Freedom of Information Act (5 USC 552), as set forth in 21 CFR 20.

Summary of the Hemophilia B Dog Study (PR-017-94)

The effect of intravenous administration of recombinant human Factor IX (rhFIX) has been studied in an in vivo canine model of hemophilia B. The study was designed to provide preliminary efficacy data of rhFIX prior to commencement of clinical trials.

rhFIX (40 IU/kg) was administered by intravenous bolus injection to three hemophilia B dogs. Blood samples for coagulation profiles, whole blood clotting times, factor IX activity assays, and rhFIX antigen determination were collected prior to treatment and during the 24 hours after treatment at the following time intervals: 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 18.0, 22.0, and 24.0 hrs. The effect of administration of rhFIX on clotting parameters in this model are depicted in Table 1. As indicated by the reduction in whole blood clotting time and secondary bleeding time to within the range observed for normal dogs, hemostasis was restored in the hemophilia B dog after treatment with rhFIX.

Table 1. The effect of rhFIX on clotting parameters in hemophilia B dogs

Parameter	Hemophilia B Dogs		Normal Dogs
	Before Treatment	After Treatment with rhFIX	No Treatment
Whole blood clotting time	53 ± 10.6 min	10.3 ± 1.0 min	7.5 ± 1.5 min
Secondary bleeding time ^a	> 15 min	2.6 ± 0.5 min	3.5 ± 2.5 min
Partial thromboplastin time	125 ± 25 sec	60.5 ± 15 sec	37.5 ± 1.5 sec

^aTime for a clot to form after induction of blood flow by wiping away the primary clot from the site of a dog toenail clip.

Based on antigen analysis, it was determined that the clearance of rhFIX from plasma was biphasic. The distributional half-life was 0.38 ± 0.33 hours and the elimination half-life was 11.4 ± 1.4 hours. The PK values reported for rhFIX are comparable to those obtained with human plasma-derived factor IX in normal Beagle dogs (For a detailed description of the studies in normal Beagle dogs, see letter to Marlene Haffner, July 15, 1994, Attachment A).

In summary, the results indicate that rhFIX can effectively restore normal hemostasis in a canine model of hemophilia B. The pharmacokinetic behavior of the recombinant product is similar to the plasma-derived human protein.

Genetics Institute, Inc.

87 CambridgePark Drive
Cambridge, Massachusetts 02140
Telephone (617) 876-1170
Telefax (617) 876-0388

GENETICS  INSTITUTE

Recombinant Human Factor IX (rhFIX)
Orphan Drug Application
Ref. No. 94-822

July 15, 1994

Marlene Haffner, M.D., M.P.H.
Office of Orphan Products Development
(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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JUL 18 1994

6 EKM
7/18/94

Dear Dr. Haffner:

Office of Orphan Products Development

Thank you for your letter of May 11, 1994 acknowledging review of our orphan drug application for recombinant human Coagulation Factor IX (rhFIX). As requested, we are responding within the 90-day period to your inquiry concerning our manufacturing and testing process for our Chinese hamster ovary (CHO) cell line and the half-life of rhFIX in dogs. First, it is important to note that the reported nonclinical information was obtained in our own studies, and not elsewhere. Second, the rhFIX characterized in the studies was manufactured by Genetics Institute at our Andover facility. Descriptions and results of the completed preclinical laboratory studies are summarized on the following pages. A manuscript for publication, entitled "Evaluation of Recombinant Human Factor IX: Pharmacokinetic Studies in the Rat and Dog," which describes the studies in more detail, is reproduced here as Attachment A. We hope the information provided in this letter is sufficient to complete your review of our Orphan Drug Application.

As was stated in Section 7 of our Orphan Drug Application

we intend clinical testing of the drug to begin in patients in early 1995.

We anticipate

Please call me at (617) 498-8623, or Maryann Krane, Senior Regulatory Affairs Associate, at (617) 498-8737, if you have any questions or require additional information.

Sincerely,



Frederick T. Gates, Ph.D.
Director, Regulatory Affairs

The information and data on this page and on all other pages marked with the following statement

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are confidential business information or trade secrets of Genetics Institute, Inc., or its licensors and are exempt from disclosure under the Freedom of Information Act (5 USC 552), as set forth in 21 CFR 20.

Summary of rhFIX Preclinical Studies

Preclinical studies with intravenous administration of recombinant human Factor IX (rhFIX) have been performed in Sprague-Dawley rats and Beagle dogs (Table 1). The studies were designed to provide preliminary pharmacologic and pharmacokinetic data of rhFIX to aid in the selection of appropriate dose and study duration in the Hemophilia B dog efficacy model and in the formal toxicology study of rhFIX in Beagle dogs.

Table 1. Preclinical laboratory studies of rhFIX

Study

28-Day Rat Pharmacology Study

28-Day Dog Pharmacology Study

Single-dose Dog PK Study of rhFIX vs. Mononine™

All of the studies described in the above table were performed by Genetics Institute, Inc., using rhFIX manufactured at Genetics Institute's Andover facility. Preliminary summaries of each study are included below. The section entitled "Single-dose PK comparison of rhFIX" is an across-study compilation of data from other studies listed in Table 1. A manuscript for publication, entitled "Evaluation of Recombinant Human Factor IX: Pharmacokinetic Studies in the Rat and the Dog," which describes the three studies in more detail, is reproduced here as Attachment A.

28-Day Rat Pharmacology Study

rhFIX (50 units/kg) was administered once daily via the tail vein to Sprague-Dawley rats for 28 days. Anti-human Factor IX antibody levels were determined in serum collected on study Days 1, 7, 14, 21, and 28. Only 1 rat developed antibodies during the 28-day period. rhFIX plasma concentrations were determined by ELISA on Days 1 and 28 of administration. Preliminary assessment of the pharmacokinetic data indicates a half-life of approximately 5.0 hr on Day 1. Plasma concentration data on Day 28, limited to 90 minutes post-dose, were slightly higher than the respective concentrations on Day 1, but no conclusions can be drawn concerning the observed difference due to the limited concentration data on Day 28 (See Attachment A, Figure 2).

28-Day Dog Pharmacology Study

A 28-day antigenicity study of rhFIX was conducted in Beagle dogs. A plasma-derived FIX product (Mononine™) was used as a study control.

rhFIX (40 units/kg) or Mononine (40 units/kg) were administered intravenously once daily to Beagle dogs for 28 or 14 days, respectively. Dogs receiving rhFIX were administered a final injection on Day 34, following a 6-day washout period. Anti-human Factor IX antibody levels were determined in serum collected from dogs treated with Mononine or rhFIX on study Days 1, 7, and 14, or Days 1, 7, 14, 21, 28, 34, and 42, respectively. Three of four dogs developed antibodies against Mononine by Day 14, and three of four dogs developed antibodies against rhFIX by Day 28. rhFIX did not appear to be any more antigenic than Mononine in the dog. Decreased appetite, especially during the first week of administration, was noted in all of the dogs receiving either Mononine or rhFIX. Two of four dogs in the Mononine group and one of four dogs in the rhFIX group had generalized reactions to the protein administration, consisting of transient weakness, tachycardia, tachypnea, and prolonged capillary refill time. All episodes resolved within minutes without treatment, and subsequent reactions failed to occur as the speed of bolus injection was decreased from 15 sec to 1 minute. These results support selection of a 14-day regimen in pharmacology and safety studies of rhFIX.

Pharmacokinetic studies of rhFIX were conducted on Days 1, 28, and 34 in the dogs which received rhFIX. Increased clearance and decreased half-life of rhFIX was observed in the dogs which developed an antibody response. The apparent half-life of rhFIX on Day 1 in all four dogs and Days 28 and 34 in the one dog with no antibodies was approximately 12 - 14 hrs.

Single-Dose Dog PK Study of rhFIX vs. Mononine

The pharmacokinetics of rhFIX were compared to plasma-derived FIX product (Mononine) after single IV doses (100 units/kg) in separate groups of normal Beagle dogs. rhFIX (n=5) and Mononine (n=3) appeared to exhibit similar plasma concentration profiles, as determined by ELISA. The estimated plasma half-lives were similar (Table 2), ranging in the individual animals from 12-14 hrs for rhFIX and from 11-15 hrs for Mononine. Peak plasma concentrations and clearance values of rhFIX and Mononine were comparable following the IV bolus dose. The approximately 25% higher AUC value observed for Mononine vs. rhFIX may be explained in part by the fact that although each dog received an identical amount of FIX in terms of activity units, due to the lower specific activity of Mononine relative to rhFIX (150 U/mg vs. 200 U/mg), the dogs injected with Mononine received 25% more protein. These preliminary findings in dogs suggest that the pharmacokinetic behavior of recombinant human FIX is similar to plasma-derived FIX.

Table 2. Preliminary Mean (\pm SE) rhFIX and Mononine PK Parameter Estimates from IV Bolus Injections (100 Units/kg) in Beagle Dogs

Product	C ₀ (μ g/mL)	AUC (μ g \cdot hr/mL)	T _{1/2} (hr)	CLT (mL/hr/kg)	V _{ss} (mL/kg)
rhFIX	4.3 \pm 0.3	35.3 \pm 2.3	13.2 \pm 1.6	14.4 \pm 1.0	222 \pm 19
Mononine	4.7 \pm 0.2	43.6 \pm 2.5	13.3 \pm 1.2	15.5 \pm 0.9	255 \pm 26

C₀, initial plasma concentration; AUC, area under concentration versus time curve; T_{1/2}, plasma-concentration half-life; CLT, total clearance; V_{ss}, steady state volume of distribution.

Single-dose PK Comparison of rhFIX

Table 3 compares preliminary pharmacokinetic data obtained from the dog studies described above. Interim analysis of the PK behavior of single 40 or 100 units/kg IV doses in separate groups of beagle dogs suggest that rhFIX plasma concentrations increased in proportion to dose over the dose range studied.

Table 3. Preliminary Mean (\pm SE) rhFIX PK Parameters in Beagle Dogs After Single 40 and 100 U/kg IV Doses

N	Dose (U/kg)	C ₀ (μ g/mL)	AUC (μ g \cdot hr/mL)	T _{1/2} (hr)	CLT (mL/hr/kg)	V _{ss} (mL/kg)
4	40	1.6 \pm 0.4	14.2 \pm 2.5	10.3 \pm 1.1	14.9 \pm 2.3	204 \pm 17
5	100	4.3 \pm 0.3	35.3 \pm 2.3	13.2 \pm 1.6	14.4 \pm 1.0	222 \pm 19

N, number of animals tested; see Footnote to Table 2 for explanation of other abbreviations.

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GENETICS  INSTITUTE

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Office of Orphan Products Development

TO SKM 4/8/94

April 7, 1994

Marlene Haffner
Office of Orphan Products Development
(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

On behalf of Genetics Institute, Inc. and in accordance with Section 526 of the Food, Drug and Cosmetic Act, enclosed with this letter, in duplicate, is a request for orphan drug designation for coagulation Factor IX (recombinant), also referred to as recombinant human Factor IX (rhFIX).

Recombinant human Factor IX is currently under development at Genetics Institute for the treatment of Hemophilia B in human subjects; in December, 1994, we expect to file with FDA an application for an Investigational New Drug exemption for rhFIX.

Sincerely,

Frederick T. Gates III

Frederick T. Gates, Ph.D.
Director, Regulatory Affairs

Encl.

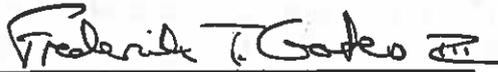
REQUEST FOR ORPHAN DRUG DESIGNATION:

COAGULATION FACTOR IX (RECOMBINANT)

[The following information is presented in the format as provided in 21 CFR § 316.20]

1. **A statement that the sponsor requests orphan-drug designation for a rare disease or condition, which shall be identified with specificity.**

Genetics Institute, Inc. ("The Sponsor") requests orphan drug designation for Coagulation Factor IX (Recombinant) for the treatment of Hemophilia B.



Frederick T. Gates
Director, Regulatory Affairs

April 7, 1994
Date

2. (i) **Name and address of the Sponsor;**

Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140

- (ii) **Name and address of the sponsor's primary contact person;**

Frederick T. Gates, Ph.D.
Director, Regulatory Affairs
Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140

Maryann Krane
Senior Regulatory Affairs Associate
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- (iii) **The generic and trade name, if any, of the drug or drug product;**

Generic name: coagulation Factor IX (recombinant).

No trade name has been established for the drug.

- (iv) The name and address of the source of the drug if it is not manufactured by the sponsor.

3. A description of the rare disease or condition for which the drug will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed.

The disease

Hemophilia B, or Christmas disease, is an X-linked recessively inherited disorder of blood coagulation characterized by insufficient or abnormal synthesis of the blood clotting protein Factor IX. Activated Factor IX, in the presence of activated Factor VIII, is required for activation of Factor X. Activated Factor X subsequently converts prothrombin to thrombin, which catalyzes the cleavage of fibrinogen to fibrin, resulting in the formation of a fibrin clot. Depending on the level of biologically active Factor IX the patient is able to produce, clinical symptoms after surgery or trauma range from only moderate skin bruising or excessive hemorrhage to spontaneous hemorrhage into joints, muscles or internal organs including the brain. Severe or recurring hemorrhages can produce orthopedic deformity, organ dysfunction, or death (Levine, 1987). Approximately 50% of patients have a mild course with only occasional bleeding problems; the 20% of patients diagnosed with severe Hemophilia B have frequent bleeding and sufficiently severe problems to warrant regular prophylactic Factor IX replacement therapy.

The proposed indication and reason for therapy

The anticipated use for recombinant human Factor IX is the correction of the coagulation deficit in congenital Hemophilia B, or Factor IX deficiency. Addition of biologically active Factor IX to replace the deficiency reconstitutes the patient's ability to form a clot and to control bleeding. This product will provide specific and definitive replacement of the Factor IX that is deficient in patients with Hemophilia B. It will be indicated for replacement treatment to control and to prevent the hemorrhagic complications of Hemophilia B, including spontaneous bleeding events, bleeding from contemplated or performed surgery, bleeding from trauma, and recurring bleeding in patients who have had numerous joint or soft tissue bleeding in the past, leading to or potentially leading to orthopedic deformities and associated morbidity.

Treatment with replacement Factor IX can be used effectively to stop hemorrhages and hemarthroses. Standard textbooks of hematology and medical practice recommend that a blood level of 15 to 40% of normal Factor IX activity is sufficient to arrest minor bleedings and prevent their progression; for more serious bleeding or surgery a higher

level of up to 60 to 100% may be required (Bell and Jackson, 1988; Roberts et al., 1990; Menitove, 1990; Linker, 1991).

4. **A description of the drug and a discussion of the scientific rationale for the use of the drug for the rare disease or condition, including all data from nonclinical laboratory studies, clinical investigations, and other relevant data that are available to the Sponsor, whether positive, negative, or inconclusive. Copies of pertinent unpublished and published papers are also required.**

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(11-15 hrs, n=3).

Factor IX replacement therapy for Christmas disease, or Hemophilia B, is a long-established primary therapeutic intervention. Currently available treatments consist of the use of lyophilized plasma-derived prothrombin complex concentrates or chromatographically purified plasma-derived human Factor IX. Some brand names are Prothromplex TIM4™, Immunine™, Proplex™, Profilnine™, Alphanine®SD, and Mononine™. None of these therapeutics has been able to address the needs of the entire Hemophilia B patient population. The perceived disadvantages of each product class as well as selected factor IX products are listed in Tables 1 and 2. The use of prothrombin complexes has long been associated with a small but definite risk of thromboembolic complications and disseminated intravascular coagulation (Fyman et al., 1985, Small et al., 1982, Chavin et al., 1988). Despite assertions of superiority of Mononine relative to preexisting commercial preparations of Factor IX, Mononine has not gained universal acceptance by users. The risk of infection with human virus or nonviral pathogens from a blood-derived product such as Mononine cannot be totally eliminated (See Tables 1-3, and Section 5 for details). Consequently, prescription and use of such blood-derived products must consider this potential for contamination. The availability of a recombinant DNA-derived Factor IX preparation will provide physicians and patients alike a guarantee

of freedom from blood-borne viral contamination, allowing the treatment of Hemophilia B to be unencumbered by any need for a risk analysis for blood-borne viruses or other nonviral contaminants of human plasma. As a result, patients will be able to more fully address their medical needs with respect to Factor IX. According to the National Hemophilia Foundation,

Not only do these [recombinant Factor IX] products offer the potential of improved safety, but also, they open the door to the possibility of exciting new therapies. For example, as confidence in product safety increases, the willingness to treat on a preventive prophylactic basis (rather than episodic as it is now) is greatly increased. With effective prophylaxis, it would then be possible for newly diagnosed children not to experience spontaneous bleeding episodes. This in turn would be very important in helping to prevent painful and disabling joint damage (National Hemophilia Foundation, 1994).

5. Where the sponsor of a drug that is otherwise the same drug as an already-approved orphan drug seeks orphan-drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug.

Mononine and Alphanine (but not Alphanine SD) are Factor IX products that have already received orphan drug designation. Recombinant human Factor IX may be clinically superior to the already-approved Factor IX orphan drugs for any of the following reasons:

The use of recombinant human Factor IX eliminates the risk of transmitting blood-derived pathogens;

No monoclonal antibody is used in the purification of the recombinant human Factor IX preparation, so that it may be used freely in patients who might be allergic to mouse proteins;

The use of recombinant human Factor IX does not involve the risk of thrombosis or disseminated intravascular coagulation that is associated with co-administration of other contaminating coagulation factors.

Each of the above claims of superiority are treated separately in the following subsections A through C.

A. The use of recombinant human Factor IX eliminates the risk of transmitting blood-derived pathogens

All currently available Factor IX preparations are blood-derived products. "The potential risk of viral transmission is a critical consideration in the development of coagulation factor concentrates derived from pooled human plasma" (Clinical Profile: Mononine). There is risk that prior to purification all plasma-derived products have been in contact with human viruses associated with adverse effects (e.g. HIV, Hantavirus, and Hepatitis A, B, C), as well as deleterious nonviral contaminants. *Although sincere and state-of-the-art efforts have been made to reduce the risk of viral transmission by better plasma screening, improved purification, and advanced inactivation procedures, the risk of transmission of untested, poorly understood, or previously unknown viruses or other plasma-derived contaminants cannot be eliminated from plasma-derived Factor IX products.* Such concerns were recently the subject of a Blood Products Advisory Committee meeting (September 23-24, 1993) at which an entire day was devoted to the discussion of blood product transmission of Hepatitis A and other non-lipid-enveloped viruses such as parvovirus. The topic was revisited only six months later by the committee in conjunction with a workshop on "The Role of Virus-Inactivated Plasma in Clinical Medicine" (March 23, 1994), sponsored by the Food and Drug Administration in conjunction with the National Heart, Lung, and Drug Institute, the American Association of Blood Banks, the American Red Cross, the Council of Community Blood Centers, and the Armed Services Blood Program. The issue of risk of viral transmission through blood and blood derivatives clearly is an active concern of U.S. health and regulatory agencies and their counterparts in many other countries. The risk of contamination of the blood supply with viruses and other pathogens is indicated by the existence of the FDA's elaborate system of precautions and the recall of more than 1% of all blood and blood products during the years 1991 and 1992 (Revelle, May 3, 1993). As recently as November, 1993, the Canadian Red Cross had to notify all hospital blood banks and hemophilia treatment programs to check their inventories for lots of a Factor IX Complex (Human) manufactured from plasma which may not have been adequately tested for HIV (HPB Press Release, November 19, 1993). According to a recent evaluation of the viral safety of coagulation factors VIII and IX, despite all efforts to reduce the risk of viral transmission from blood products, no plasma-derived coagulation factor concentrate can be considered virus-free (Mannucci, 1993).

Recent cases of contamination of blood-derived coagulation factors with parvovirus. Infections with the non-lipid-enveloped B19 parvovirus have developed in a number of Hemophilia A patients infused with a solvent/detergent-treated concentrate (Azzi et al., 1992). Subsequent analysis of 25 different brands of clotting factor concentrates using polymerase chain reaction (PCR) technology demonstrated that nearly a third of these clotting factor concentrates were found to be positive for B19 DNA. The B19 DNA-positive concentrates included a solvent/detergent-treated factor IX product (Biotransfusion), and a monoclonal antibody-purified Factor VIII product (Monoclote, Armour) (Zakrzewska, 1992). Currently, human plasma is not screened for B19 parvovirus contamination, and the Mononine purification process has not been

specifically validated for the removal of B19 parvovirus.

Recent cases of contamination of blood-derived coagulation factors with Hepatitis A. An outbreak of infection with Hepatitis A virus, another non-lipid-enveloped virus, occurred in 88 hemophiliacs in Europe, all treated exclusively with the solvent/detergent-inactivated factor VIII concentrates Emoclot Octa VI (Aima Derivati) or Octavi (Octapharma) (Mannucci, 1992; Gerritzen et al., 1992; Temperley, 1992). Hepatitis A virus RNA subsequently was detected in two of four batches of the Octapharma concentrate; one of the two positive batches had been administered to 4 of the hemophiliacs who developed acute Hepatitis A virus infection (Normann et al. 1992). Currently, human plasma is not routinely screened for Hepatitis A contamination.

Recognized risk of contamination of blood-derived coagulation factor with nonA, nonB hepatitis. Patients using Mononine are warned of the risk of blood-derived virus transmission, particularly nonA, nonB hepatitis (Package insert, Mononine: Warnings).

Recent case of recall of blood products because of Hepatitis C infection. On February 24, 1994, manufacture of the blood-derived immune globulin products Gammagard™ and Polygam™ was voluntarily discontinued and immediate market withdrawals were initiated because of safety concerns after clusters of patients receiving Gammagard became infected with the lipid-enveloped virus Hepatitis C. Polygam was recalled because its manufacture used the same facilities and production methods for making Gammagard, although not the same plasma pools (The Associated Press, 1994). This most recent report of potential viral infection through the use of a blood-derived product further underscores the present potential safety risks associated with blood-derived protein therapeutics.

Recognition of the inherent risk of blood-derived products. Despite efforts to demonstrate safety of the clotting factor concentrates with respect to viral contamination (Nowicki et al., 1993), concerns about the potential for infectivity are reflected in warnings such as the following, contained in the package insert of the already-approved Factor IX drug Mononine:

This product is prepared from pooled human plasma which may contain the causative agents of hepatitis and other viral diseases. Prescribed manufacturing procedures utilized at the plasma collection centers, plasma testing laboratory, and the fractionation facility are designed to reduce the risk of transmitting viral infection. However, the risk of viral infectivity from this product cannot be totally eliminated.

Accordingly, the benefits and risks of treatment with such concentrates still require careful assessment prior to use. Recombinant human Factor IX will carry no such risk of contact with plasma-derived viruses or other plasma-derived contaminants, and therefore will be a product of greater purity and safety than presently available products.

Recognition of the superiority of recombinant vs. blood-derived Factor IX. The above claim for superiority of recombinant Factor IX vs. blood-derived Factor IX is consistent with the remarks of FDA Commissioner David A. Kessler concerning the approval of Genetics Institute's other recombinant coagulation factor, Factor VIII [Antihemophilic Factor (Recombinant)]:

The production of factor VIII by recombinant DNA technology eliminates even the theoretical possibility of the transmission of viruses from plasma. Its approval is a milestone in the history of treatment of hemophilia (USDHHS Press Release, December 10, 1992).

The recognition of superiority of recombinant Factor VIII was recently repeated in an FDA talk paper:

The recombinant DNA technology eliminates even a theoretical possibility of the transmission of viruses from plasma (Revelle, March 1, 1993).

In a recent review of Factor IX concentrates for clinical use, Arthur R. Thompson, M.D., Ph.D. (Puget Sound Blood Center and University of Washington) concluded:

More definitive viral safety would clearly be attained with a recombinant, or synthetic, Factor IX (Thompson, 1993).

The medical literature contains additional recommendations for developing recombinant coagulation factors:

Currently hemophilia B is treated by plasma protein replacement therapy. Although effective, this exposes patients to potential risks, such as hepatitis or HIV infection. The cloning of the factor IX gene raises prospects for developing safer therapies (Kurachi et al., 1991).

The main problems in the treatment of hemophiliacs include the viral and immunological safety of factor concentrates.... The current status of haemophilia therapy could shortly be changed by the application of recombinant genetic techniques (Bloom, 1991).

In a recent clinical evaluation of viral safety of coagulation factors, Dr. Pier Mannucci (Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Maggiore Hospital, and University of Milan, Italy) asserted the following:

Recombinant factor VIII should carry no risk of transmitting blood borne viruses (Mannucci, 1993).

He also noted that recombinant coagulation factors carry a theoretical risk of transmission

of viruses that might be associated with the mammalian cell cultures used to produce them, the bovine proteins that may be used in the cell culture medium and any murine monoclonal antibodies used to purify the coagulation factors. However, in contrast to the history of contamination of blood-derived products by deleterious viruses, there has been no report of adverse events resulting from the use of recombinant therapeutic proteins that are attributed to viruses associated with any Chinese hamster ovary cell culture process used for their production. The Chinese hamster ovary cells used for the production of recombinant human Factor IX and other recombinant products have been extensively tested for a large number of viruses and infectious agents and have been demonstrated to be free of any contaminating infectious agent. In addition, as stated previously (Section 4, above), no monoclonal antibodies nor murine or bovine materials of any kind are involved in the production of Genetics Institute's recombinant human Factor IX.

Finally, the National Hemophilia Foundation strongly urges the development of a recombinant form of Factor IX:

Because recombinant products are not dependent upon human source plasma, the NHF believes that recombinant technology offers the potential of improved safety. Having a product that is truly free of any human viruses that can be transmitted through the dozens of infusions required each year by people with severe factor IX deficiencies would be an important step forward, particularly when you consider the damage that has been done to the hemophilia community as a result of HIV and hepatitis (National Hemophilia Foundation, 1994).

B. No monoclonal antibody is used to purify recombinant human Factor IX preparations.

As described in Section 4 above, the purification of recombinant human Factor IX does not use an immunoaffinity chromatography step. In contrast, purification of Mononine involves the use of an immunoaffinity chromatography step resulting in contact with and detectable contamination by murine protein. For this reason, known hypersensitivity to mouse protein is a contraindication to Mononine (Ref: Package insert: Mononine: Contraindication). This contraindication does not apply to recombinant human Factor IX.

C. The use of recombinant human Factor IX does not involve the risk of thrombosis or disseminated intravascular coagulation that is associated with co-administration of other contaminating coagulation factors.

Thrombosis or disseminated intravascular coagulation (DIC) has been observed to follow administration of Factor IX complex concentrates which contain amounts of Factors II, VII, and X. Despite the increased purity of the orphan drug Mononine relative to earlier Factor IX products, physicians still are warned of such risks when administering Mononine:

Patients given Mononine™ should be observed closely for signs or symptoms of intravascular coagulation or thrombosis. Because of the potential risk of thromboembolic complications, caution should be exercised when administering this concentrate to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with Mononine™ should be weighed against the risk of these complications (Package insert: Mononine: Precautions).

There is not even a theoretical possibility of contamination of recombinant human Factor IX with other coagulation factors.

6. **Where a drug is under development for only a subset of persons with a particular disease or condition, a demonstration that the subset is medically plausible.**

Recombinant human Factor IX is appropriate for use by all patients who have the coagulation deficit in congenital Hemophilia B.

7. **A summary of the regulatory status and marketing history of the drug in the United States and in foreign countries, e.g., IND and marketing application status and dispositions, what uses are under investigation and in what countries; for what indication is the drug approved in foreign countries; what adverse regulatory actions have been taken against the drug in any country.**

Recombinant human Factor IX is currently under development at Genetics Institute for the treatment of Hemophilia B in human subjects;

8. Documentation, with appended authoritative references, to demonstrate that:

- (i) the disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in § 316.21 (b).

The estimates of those afflicted with Hemophilia B in the United States range from approximately 2,800 to 6,000:

Based on the incidence of the disease reported in current textbooks of hematology and assuming a current US population of 260 million people of which 48.8% are male (Statistical Abstract of the U.S., 1993), the estimates of those afflicted with Hemophilia B in the United States range between a minimum of 3,900 (Levine, 1987) to 4,200 (Hedner and Davie, 1987) and a maximum of 5,200 (Levine, 1987; Roberts and Jones, 1990).

According to the National Hemophilia Foundation (1993), a prevalence study entitled "Blood Resources Studies" was conducted by the National Heart and Lung Institute in 1972. Based on information from this study the foundation estimated that 2,800 persons are afflicted with Hemophilia B in the United States.

The highest reported incidence of Hemophilia B in a given country is 2.3 per 100,000 in Ireland (Etzler, 1992). Application of this recorded maximum incidence of Hemophilia B to calculate a potential maximum incidence for the United States yields a theoretical upper limit of approximately 6,000 persons afflicted with Hemophilia B in the United States.

Regardless of which source is deemed more appropriate, a patient population of less than 200,000 clearly has been established.

- (ii) For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in § 316.21 (c).

Because recombinant human Factor IX is intended for diseases or conditions affecting fewer than 200,000 persons in the United States (See Section 8(i), above), this section does not apply.

9. **A statement as to whether the Sponsor is the real party in interest of the development and the intended or actual production and sales of the product.**

Genetics Institute, Inc. is the real party in interest of the development and the intended production and sales of the product recombinant human Factor IX.

Table 1. Perceived disadvantages of commercially available Factor IX products.

Factor IX product class	Perceived class disadvantages
<p>Crude complexes Examples: Bebulin VH (Immuno) Faktor IX HS (Behringwerke) Konyne 80 (Bayer/Miles) Profilnine HT (Alpha) Proplex (Baxter/Hyland)</p>	<p>Contain significant amounts of coagulation factors II, VII and X. Small but definite risk of thromboembolic complications. Risk of blood-derived virus and nonviral pathogen transmission.</p>
<p>Activated complex Examples: Autoplex (Baxter) FEIBA (Immuno)</p>	<p>Contain significant amounts of coagulation factors II, VII and X. Small but definite risk of thromboembolic complications. Risk of blood-derived virus and nonviral pathogen transmission.</p>
<p>Purified product Examples: AlphaNine SD (Alpha) Coagulation FIX (Baxter/ARC) FIX SD HP (Bio-Transfusion, France) High purity IX (Cent. Fract. Sanguine, Canada) Highly purified IX (Kabi, Sweden) Immunine (Immuno) IX-HP (Netherlands Red Cross) Mononine (Armour) Nanotiv (Kabi Pharmacia) Preconativ (Kabi Pharmacia) Prothromplex TIM4 (Immuno)</p>	<p>Risk of blood-derived virus and nonviral pathogen transmission. [The risk was confirmed recently by detection of Parvovirus B19 DNA by PCR in Bio-Transfusion's FIX SD HP (Zakrzewska, 1992).]</p>

Table 2. Perceived disadvantages of the currently marketed Factor IX orphan drug Mononine.

Detectable contamination with mouse protein (Package insert).

Risk of blood-derived virus transmission, particularly nonA, nonB hepatitis (Package insert: Warnings).

B19 parvovirus, Hantavirus, Hepatitis A, B or C not used in virus-removal validation.

No routine testing of plasma pools for B19 parvovirus, Hantavirus, or Hepatitis A.

Risk of intravascular coagulation (Package insert: Warnings, Precautions).

Table 3. Safety issues associated with the virucidal methods applied to Factor IX products.

Virucidal method	Safety issues associated with the virucidal method [†]	Factor IX products employing the virucidal method
Dry heat, 80°C, 72 h	Incomplete inactivation of B19 parvovirus (ref. in Mannucci et al. 1993).	Konyne 80
Dry heat, 60°C, 144 h	No available prospective studies. Cases of HIV and hepatitis transmission observed when heating limited to 72 h. (ref. in Mannucci et al., 1993).	Proplex, Autoplex
Heating in solution (pasteurization), 60°C, 10 h	Antibodies to parvovirus B19 detected in patients (Azzi et al., 1992). Five cases of Hepatitis B or C (Mannucci et al., 1993; Gerritzen et al., 1993).	Faktor IX HS
Vapor heat	In an early prospective study of vapor heat-treated FIX, 4 of 28 patients developed Hepatitis B; one patient also developed Hepatitis C (referred to in Mannucci et al., 1993).	Bebulin VH* FEIBA* Immunine ⁺ Prothromplex TIM4 ⁺
Heating in suspension (n-heptane), 60°C, 20 h	5 cases of hepatitis reported in factor VIII and factor IX concentrates manufactured by Alpha (referred to in Mannucci et al., 1993).	Profilnine HT AlphaNine
Solvent /detergent (TNBP and Tween 80, or Triton X-100, or cholate)	Antibodies to parvovirus B19 detected in patients (Azzi et al., 1992). 88 cases of Hepatitis A infection (Mannucci, 1992; Gerritzen, 1992; Temperley, 1992).	Coagulation FIX FIX SD HP (Bio-Transfusion) Highly purified IX (Green Cross) IX-HP Nanotiv AlphaNine SD
Sodium thiocyanate plus ultrafiltration	No available prospective studies.	Mononine

[†] For a general review of viral safety issues related to coagulation factors see: Thompson, 1993; Mannucci, 1993.

* 60°C, 10 h, 1160 mbar.

+ 60°C, 10 h; 80°C, 1 h.

The articles referenced herein are attached.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

February 12, 1997

Genetics Institute
87 Cambridge Park Drive
Cambridge, MA 02140

Attention: Frederick T. Gates, Ph.D.
Director, Regulatory Affairs

Dear Dr. Gates:

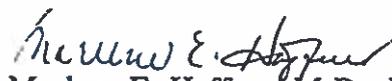
Reference is made to your orphan product BeneFix™ [Coagulation Factor IX, (Recombinant)], which was designated an orphan drug pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 360bb) on October 3, 1994 for the treatment of hemophilia B.

This letter is to inform you that as the first sponsor of Coagulation Factor IX, (Recombinant) to obtain marketing approval for this indication, you are entitled to seven years of exclusive marketing approval pursuant to Section 527 of the FFDCA (21 U.S.C. § 360cc) for the use of Coagulation Factor IX, (Recombinant) for the control and prevention of hemorrhagic episodes in patients with hemophilia B (congenital factor IX deficiency or Christmas disease), including control and prevention of bleeding in surgical settings. The exclusive seven year approval period began on February 11, 1997, the date of approval of your product licensing application (PLA 96-1048).

Thank you for your efforts in developing Coagulation Factor IX, (Recombinant) for the treatment of hemophilia B. The Orphan Drug Act and orphan product development program were established due to the realization that resources and commitment devoted to the development of drugs for "orphan" populations may not provide financial returns. It is with genuine gratitude that we recognize your efforts.

Also, please note that holders of exclusivity for approved orphan products are required to assure the availability of sufficient quantities of an orphan drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drug product's exclusive approval [21 CFR 316.36(b)].

Sincerely yours,



Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development