Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Pharmacology/Toxicology Secondary Review
Division of Hematology
Office of Blood Research & Review

TO: The file
CC: Basil Golding, M.D., Director, Division of Hematology, Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER)
Roman T. Drews, MD, PhD, Committee Chair, Laboratory of Hemostasis, OBRR, CBER

FROM: Anne M. Pilaro, PhD, Acting Chief, Toxicology Branch, Division of Hematology, OBRR, CBER

STN BLA #: 125426/000/000 (original submission), 125426/000/008, and 125426/000/010
APPLICANT: Inspiration Biopharmaceuticals Inc., Cambridge, MA
PRODUCT: recombinant, human coagulation Factor IX (IB 1001; Ixinity™) for the control and prevention of bleeding episodes in patients with hemophilia B, or for the peri-operative management of patients with hemophilia B

SUBMISSION TYPE: original BLA application, and amendments 008 and 010 containing nonclinical information
DATE: January 28, 2013

FINAL RECOMMENDATION:

I concur with Dr. Wyatt's conclusions regarding the nonclinical safety of Inspiration Biopharmaceuticals' recombinant human Factor IX (tradename Ixinity™), and his current recommendation that this new biologics licensing application **may not be approved** and a Complete Review (CR) letter should be issued to the Applicant. Specifically, the deficiency identified by Dr. Wyatt in his review of the information submitted by the Applicant to amendment 8 of the original BLA will require additional nonclinical data, to address potential safety risks of antibody development against contaminating host cell proteins from the Chinese hamster ovary cell line used to produce the drug substance. A Discipline Review comment stating that a nonclinical study to address this deficiency is required to be completed prior to approval of the product was

previously relayed to the Applicant in an electronic message from CBER dated November 29, 2012. Apart from the discipline's recommendation to issue a CR letter to the Applicant, no additional action from the pharmacology and toxicology discipline is indicated at the present time.

A brief summary of Dr. Wyatt's reviews of the original nonclinical pharmacology and toxicology data included in the original BLA application, the Applicant's proposed nonclinical studies to address the deficiency outlined above, and Dr. Wyatt's final memorandum and recommendation for this BLA is provided, below. Copies of Dr. Wyatt's reviews, with supervisory sign-off, have been conveyed to the regulatory project manager for inclusion in the final action package, and have been uploaded into the CBER electronic document room.

SYNOPSIS:
Inspiration Biopharmaceuticals, Inc. (Inspiration) has submitted an original BLA application #125486, to support approval of their Ixinity™ recombinant, human Factor IX (rFIX; IB 1001) product. The pharmacologic class for Ixinity™ is an antihemophilic blood coagulation factor IX, and its proposed indications (from the Applicant's draft labeling) are:

- The control and prevention of bleeding episodes in patients with hemophilia B
- The peri-operative management of patients with hemophilia B

In support of licensure, Inspiration conducted a series of nonclinical pharmacology, pharmacokinetics, and toxicology and safety studies with IB 1001 in murine and canine models of hemophilia B (*i.e.* mice that were genetically deleted for Factor IX, or dogs with a naturally occurring mutation/deletion of Factor IX function), and in normal rats and rabbits. A listing of the nonclinical studies included in the original BLA submission is provided as Appendix 1 to this review; these studies were reviewed by Dr. Wyatt in his mid-cycle review memorandum, which was entered into the file on September 17, 2012.

To summarize Dr. Wyatt's mid-cycle review, animals dosed with IB 1001 showed a dose-related correction of bleeding times in the mouse and dog hemophilia B models. Dosing was well-tolerated in both hemophilic and normal animals. The major toxicity identified by Dr. Wyatt in these studies was an unexpected thrombogenicity, which occurred in normal rats after repeat dosing with a clinically relevant dose of 65 IU/kg of IB 1001. Dr. Wyatt also reports in his mid-cycle memorandum that both the Applicant and the previous nonclinical reviewer for the IND assigned causality to faulty catheters used to dose the rats, and that the effect was not considered drug-related. This conclusion would appear to be supported by an additional study conducted by the Applicant, in which repeated dosing of rats with a dose of 205 IU IB 1001/kg did not reproduce the thrombogenic toxicity.

Reviewer Comment: It should be noted that normal Factor IX levels are present in non-hemophilic animals and that local coagulation at the injection site, with subsequent thrombus and/or embolus formation cannot be ruled out as a cause of the reported thrombogenicity.

The IB 1001 product is a recombinant, human protein and animals receiving repeated doses of the product develop antibodies against Factor IX that both accelerate clearance of the protein and neutralize its pro-coagulant activity. Therefore, the standard carcinogenicity bioassay (*i.e.* 2 years of daily treatment with IB 1001 in both rats and mice) is not feasible to conduct. Additionally, since IB 1001 is a protein and is not expected to directly interact with DNA, the standard battery of genotoxicity testing as recommended in the International Conference on Harmonisation (ICH) S2 guidance documents will not provide information that will address potential mutagenicity of the recombinant Factor IX, and as per the ICH S6 guidance on biotechnology-derived protein therapeutics, these studies are not required. The carcinogenicity, mutagenicity and chronic toxicity sections of the labeling will state only that these studies were not conducted and there is no information available, and proposed language will be addressed at the time of approval of this BLA.

No nonclinical reproductive or developmental toxicity studies were conducted in support of this submission. Hemophilia B is an X-linked disorder and affects only male subjects; therefore, it is highly unlikely that a pregnant or lactating woman would receive IB 1001. Upon approval, Inspiration's Ixinity™ product will receive a Pregnancy Category C (or its equivalent descriptive summary) labeling that will include a statement that nonclinical reproductive and developmental toxicity studies with Ixinity™ have not been conducted, and the product should be used only if clearly needed. This proposed labeling will be consistent with that included in prescribing information for other approved recombinant human coagulation factors for the treatment of hemophilia A or B.

During the review cycle, the Applicant notified CBER that 18 of 68 patients receiving IB1001 in ongoing clinical trials had developed measurable titers of antibody directed against host cell proteins (HCP) from the Chinese hamster ovary (CHO) cell line used to produce the drug substance. Additional nonclinical, manufacturing and clinical data were submitted to both this BLA and to IND #13551 on October 12, 2012 (STN BLA #125426/000/008 and IND #13551/065, respectively). A primary review was conducted by Dr. Wyatt and entered into the BLA and IND files on November 14, 2012, and I completed a secondary review and submitted it to the BLA and IND files on November 28, 2012. In summary, the Applicant proposed to incorporate an additional (b)(4) step in the manufacture of the IB1001 drug substance, to reduce or remove the HCP from the producer cell line and thereby reduce the immunogenic potential of the drug product. Inspiration submitted their draft protocols for studies to assess the biochemical, biophysical and potency comparability of the post-manufacturing process change IB1001 with the Ixinity™ product used in previous clinical trials. In this same submission, the Applicant also provided a draft protocol for a pharmacokinetic (PK) comparability study in rats designed to evaluate the exposure and kinetics profile of the pre-and post-(b)(4) IB1001. Dr. Wyatt's and I both found the planned nonclinical pharmacokinetic study to be appropriate to demonstrate any potential changes in exposure between the pre- and post-process change materials, and their conclusions are documented in their respective reviews. However, an additional nonclinical study was required to demonstrate that the immunogenic component had been removed by the manufacturing change, and was communicated to the Applicant in an

electronic message from CBER dated November 29, 2012. The Applicant responded with a request for additional information regarding the study design (STN BLA #125426/000/010) on December 14, 2012; however, since no protocol was included in the BLA amendment, the pharmacology and toxicology discipline (as documented in Dr. Wyatt's final review entered January 17, 2013) will defer responding to this request until a response from the Applicant to the CR letter has been received.

In conclusion, I have evaluated Dr. Wyatt's review of the primary nonclinical data submitted with the original BLA, the proposed nonclinical PK study comparing the pharmacokinetic profiles of the pre- and post-process change IB 1001 drug substances, and his recommendations for additional nonclinical studies. At the present time, I support Dr. Wyatt's and the rest of the review team's decision that this BLA may not be approved, and that a CR letter should be issued to the Applicant describing the deficiencies that led to this decision and outlining the steps forward for approval.

Appendix 1. Preclinical studies previously reviewed for this BLA application.

The following preclinical studies were submitted to the original BLA #125426, and were the subject of Dr. Wyatt's earlier, mid-cycle review (dated June 20, 2012):

1. Evaluation of a novel human recombinant Factor IXX preparation in a canine model of hemophilia B. Study #IB1001-PT-019.
2. Thrombogenicity evaluation of IB1001, Benefix and Mononine following a single intravenous administration in (b)(4) rats. Study #IB1001-PT-010.
3. Thrombogenicity evaluation of IB1001 following a single intravenous administration in (b)(4) rats. Study #IB1001-PT-011.
4. Thrombogenicity of Factor IXaβ following a single intravenous administration in (b)(4) rats. Study #IB1001-PT-018.
5. 24-hour evaluation of the plasma pharmacokinetics of six Factor IX samples following a single intravenous dose to (b)(4). Study #IB1001-PT-016.
6. 24-hour evaluation of the plasma pharmacokinetics of six Factor IX samples following a single intravenous dose to (b)(4). Study #IB1001-PT-017.
7. Pharmacokinetic properties of IB1001 drug substance in normal rats: Comparison between "original", "refined", and "commercial" cGMP manufacturing processes. Study #IB1001-PT-R-022.
8. 14-day evaluation of the safety of Inspiration Biopharmaceuticals Factor IX following a single intravenous administration in (b)(4) rats. Study #IB1001-PT-005.
9. 14-day evaluation of the safety of Inspiration IB1001, Benefix and Mononine following a single intravenous administration in (b)(4) rats. Study #IB1001-PT-009.
10. 14-day evaluation of the safety of Inspiration Biopharmaceuticals Factor IX following a single intravenous administration in (b)(4) dogs. Study #IB1001-PT-006.
11. 28-day evaluation of the safety of Inspiration Biopharmaceuticals Factor IX following repeat intravenous administration in (b)(4) rats. Study #IB1001-PT-008.
12. Local tolerance evaluation of Inspiration Biopharmaceuticals Factor IX. Study #IB1001-PT-007.
13. Local tolerance of Inspiration Biopharmaceuticals Factor IX. Study #IB1001-PT-021.

According to the Applicant and based on the information provided in the study reports cited above and reviewed previously by Dr. Wyatt, all *in vivo* pharmacology, pharmacokinetics, single- and repeat-dose toxicology testing of IB1001 met the criteria to demonstrate the nonclinical safety and biologic activity of Ixinity™, and support its intended clinical use.