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

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

To:	BLA 125426/000/010 (cross-reference: IND 13551, amendment 67)
Reviewer:	M. Keith Wyatt, PhD, Pharmacologist, CBER\OBRR\DH
Through:	Anne M. Pilaro, PhD, Supervisory Toxicologist, CBER\OBRR\DH
Applicant:	Inspiration Biopharmaceuticals
Product:	IXINITY™ (IB 1001, recombinant human Factor IX)
Purpose:	Final BLA memo, Pharmacology/Toxicology
Date:	BLA submitted April 5, 2012

Final recommendation

The Applicant has not provided adequate nonclinical data to fully evaluate the safety of IXINITY™ (IB 1001, recombinant human Factor IX) and as a result, BLA 125426 cannot be approved during this cycle. The Applicant was previously requested (IND 13551, amendment 59 and STN BLA 125426/000/008; letter dated November 29, 2012) to provide results from in vivo nonclinical immunogenicity studies that demonstrate their additional protein purification procedure reduces host cell protein impurities to levels that will not invoke the formation of anti-CHO cell protein antibodies in animals at clinically relevant, IB1001 DP doses.

Letter-ready (CR) comment

You have not provided adequate nonclinical data to fully evaluate the safety of IXINITY™ (IB 1001, recombinant human Factor IX) and as a result, BLA 125426 cannot be approved during this cycle. Before a future BLA for IXINITY™ can be approved, please conduct and submit the results from the nonclinical in vivo immunogenicity studies detailed in the letter sent to you on November 29, 2012. The results of the nonclinical studies should demonstrate that CHO host cell protein impurity levels in the post-process IXINITY™ (b)(4) are at acceptable levels, and will not invoke immune responses or the formation of anti-CHO cell protein antibodies at the expected human dose.

Synopsis

Inspiration Biopharmaceutical, Inc. has developed a recombinant human Factor IX drug product (IXINITY™; also referred to as IB1001 DP) for use as on-demand or prophylaxis treatment of hemophilia B at a dose of 75 IU/kg. To support the approval of IXINITY™ for its intended indications, the Applicant submitted nonclinical results in the BLA suggesting that IB1001 DP was safe at the proposed clinical dose and would not present an unacceptable risk to patients. A complete review of the nonclinical data contained in these study reports was provided at the time of the mid-cycle review for this BLA. No additional nonclinical studies were provided by the Applicant for review.

During the first review cycle for STN BLA 125426/000, the Applicant informed FDA that elevated protein impurity levels from the Chinese Hamster Ovary (CHO) cells used to manufacture IB1001 DP were identified in the final product. A root cause analysis determined that (b)(4) corresponded with the increased impurity levels. Elevated impurity levels also correlated with an increased incidence in the formation of anti-CHO cell protein antibodies in patients administered IB 1001 DP under IND 13551. While the increased anti-CHO antibody titers were not associated with any adverse or severe adverse events, the presence of these antibodies was considered a potential safety concern and IND 13551 was placed on clinical hold on July 5, 2012.

To reduce the elevated CHO cell impurity levels, the Applicant modified the IB 1001 purification protocol to include a "polishing" step using a . The Applicant proposed conducting both comparability and nonclinical PK studies with the "polished" and pre-change IB 1001 (b) (4), to characterize the effects of removing the CHO cell protein impurities. FDA also recommended that an additional immunogenicity study be conducted in rabbits repeatedly administered "polished" IB 1001 to further establish that CHO cell protein impurities were at acceptable levels. A review of the proposed manufacturing changes and nonclinical PK testing protocol was submitted in STN BLA 125426/000/008, and a request for additional, recommended nonclinical studies was sent back to the Applicant on November 29, 2011 (please see the pharmacology and toxicology review for this amendment to the BLA, for the full text of the comment sent).

The Applicant submitted an amendment containing their response to STN BLA 125426/000/0010 and IND 13551, amendment 67 on December 17, 2012 which has been excerpted and presented below. FDA will consider the Applicant's concerns regarding the conduct of the rabbit immunogenicity study during review of the Applicant's resubmission in the next BLA review cycle. No further action is indicated at this time.

Applicant's response sent to FDA on December 17, 2012

We are currently discussing study designs with experts on a rabbit immunogenicity study and may wish to seek additional clarification from FDA before a protocol can be prepared. One concern is that the rabbits may develop an immunogenic response to the recombinant factor IX protein, which is present in much higher levels than the host cell proteins. We hope that FDA will be amenable to this possibility.