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 125426/000/009 (Cross reference: IND 13551)
Reviewer:	M. Keith Wyatt, PhD, Pharmacologist, CBER\OBRR\DH
Through:	Anne M. Pilaro, PhD, Supervisory Toxicologist, CBER\OBRR\DH
Applicant:	Cangene Corporation, Winnipeg, Alberta, Canada (formerly Inspiration Biopharmaceuticals)
Product:	IXINITY™ (IB 1001), recombinant human Factor IX
Purpose:	Review of a proposed nonclinical immunogenicity study in rabbits to establish reduced anti-host cell protein antibody formation following the administration of "modified" IB 1001, purified using (b)(4)
Date received:	May 7, 2013

Recommendation

The Applicant's proposed immunogenicity study in rabbits is adequately designed to address potential antibody formation, previously observed in patients, against host cell protein (HCP) impurities that may still persist in IB 1001 after purification (referred to by the Applicant as the "modified" version) using (b)(4) . In addition, the proposed pharmacokinetic (PK) study, which will be conducted simultaneously in the same rabbits, is also considered adequate to assess any potential differences in IB 1001 exposure before and after (b)(4) .

Applicant requests for clarification #1-3, sent to FDA on May 7, 2013

1) It is well established that subcutaneous administration can influence the rapid production of antibody response to immunogenic proteins compared to intravenous route of administration. However, Cangene is proposing to use repeat IV route of administration to mimic the clinical scenario. Does the agency agree with this approach?

FDA follow-up response to be sent to the Applicant

Yes, we agree that intravenous administration of IB 1001 produced by the former and modified commercial processes to rabbits is appropriate to use in your proposed study.

2) Is the current proposed study design with intravenous administration of 0.5 mg/kg dose at 2x/wk for 12 weeks with IB1001 (estimated concurrent dose of HCP at 22-44,000 and 21-30 ng/mg with former commercial and modified commercial process, respectively) adequate to address the effective removal of immunogenic components in the HCP from the Chinese hamster ovary cells used to produce IB1001?

FDA follow-up response to be sent to the Applicant

Your proposal to administer the former and modified versions of IB 1001 by twice weekly dosing of 0.5 mg/kg/dose for 12 weeks is a reasonable study design to assess the potential immunogenicity of residual amounts of Chinese hamster ovary HCP that may remain in the drug product after (b)(4) .

3) Although rabbits are a highly immunoreactive species, extremely low levels of HCP present in the drug product produced from the modified may not be sufficient to induce an immune response even after repeat administration. If there is a rapid antibody response with high incidence in the rabbits given drug product produced from the former process by 4 weeks and no response in the rabbits given product from the modified process indicating insufficient immunogenic components in the IB1001 dose to produce an immune response, the study will be stopped at 8 weeks. Does the Agency agree with this approach?

FDA follow-up response to be sent to the Applicant

Yes, we agree that your study can be terminated at 8 weeks provided that the rabbits administered IB 1001 produced by the former commercial process develop a positive antibody response at 4 weeks.

Additional letter ready comment to be sent to the Applicant

1. Please provide a more complete description of the (b)(4) procedure that will be used to evaluate rabbit plasma for the presence of anti-HCP antibodies. Specifically, please include a description of the (b)(4) for the antibodies against the CHO HCP, and identify any positive controls that will be used.

Introduction

In an amendment submitted to BLA 125426/0, Sequence 0002 on May 30, 2012, the Applicant provided results demonstrating that elevated host cell protein (HCP) levels, originating from Chinese hamster ovary (CHO) cells, in the IB 1001 drug product correlated with an increased incidence in the formation of anti-HCP antibodies by patients receiving IB 1001 treatment. While the increased anti-HCP titers were not associated with any adverse or severe adverse events in patients, the presence of these HCPs and the resulting antibody response in IB 1001 treated patients was considered a potential safety concern. To address the elevated HCP levels in the IB 1001 drug product, the Applicant conducted a root cause analysis, and has subsequently modified the (b)(4) protocol to include an additional step using a (b)(4). Product (b)(4) (b)(4) is referred to as the "modified" version. Product manufactured using the original manufacturing process without (b)(4) is referred to as the "former" version.

To determine the effect that (b)(4) may have on the quality of the modified version of IB 1001, the Applicant proposed conducting comparability (CP) and nonclinical PK studies. FDA also requested that a comparative immunogenicity study be conducted in rabbits administered the former and modified versions of IB 1001, to further ensure the reduction in the immunogenic components in the IB 1001 final drug product (i.e. HCP) by (b)(4). FDA made the request for this additional immunogenicity study in correspondences to the Applicant dated November 29, 2012 and February 1, 2013.

Herein follows a review of the Applicant's proposed nonclinical comparative immunogenicity study, which also includes a pharmacokinetics (PK) evaluation, in rabbits administered the modified and former versions of IB 1001.

IMMUNE RESPONSE INDUCED BY RABBITS TO HOST CELL PROTEIN IN 1B1001 DRUG PRODUCT FOLLWING REPEAT INTRAVENOUS ADMINISTRATION (PROPOSED), submitted to FDA on May 7, 2013, (the identity of the vendor and their location was not provided), non-GLP

Purpose: To assess the immunogenic responses by rabbits to CHO HCP in the modified or former versions of the 1B1001 drug product.

Methods: Rabbits, 24/group, will be repeatedly administered the modified or former versions of the 1B1001 drug product at a dose of 0.5 mg/kg twice weekly by the intravenous route, for up to 12 weeks. Plasma samples will be collected on day 0 (prior to dosing) and on days 28, 56 and 84. The plasma samples will be evaluated for the formation of anti-HCP antibodies using a validated (b)(4).

PK analysis will be conducted on plasma collected from six rabbits at 1, 2, 4, 8 and 12 hrs after dosing on day 0. PK analysis will be repeated thereafter on plasma samples collected after dosing once a week for four weeks. The Applicant has proposed terminating the entire study at 8 weeks if rabbits administered the former version of IB 1001 begin developing an immune response at 4 weeks. Hematology and coagulation

times will be assessed on blood samples collected from all surviving rabbits at the end of the study.

Results: The results from the (b)(4) will be reported as the incidence of anti-HCP formation, and mean population titers of binding anti-HCP antibody. The methods used to assess and report PK data were not provided in the proposed study.

Additional reviewer comments (for internal discussion only)

1). In the past, the Applicant demonstrated that patients administered IB 1001 produced by the former commercial manufacturing process developed anti-HCP antibodies that bound to (b)(4) . If rabbits administered IB1001 produced by the modified process develop anti-HCP antibodies, should the Applicant be recommended to identify the proteins that are bound by these anti-HCP antibodies?

2). A complete description of the (b)(4) methodology that will be used for the determination of anti-HCP antibody titers was not provided in the protocol for the proposed rabbit study. In the absence of this information, it is assumed that the Applicant will use (b)(4) . To increase the accuracy of the (b)(4), should (b)(4) be used as the (b)(4) during the (b)(4) evaluation?