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 Clinical Review
Office of Blood Research and Review

TO: The file

THROUGH: Paul D. Mintz, MD, Director, Division of Hematology Clinical Review (DHCR), Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER)

CC: Basil Golding, MD, Director, Division of Hematology Research and Review, (DHRR), OBRR, CBER

Chava Kimchi-Safarty, PhD, Committee Chair, Laboratory of Hemostasis, DHRR, OBRR, CBER

FROM: Anne M. Pilaro, PhD, Acting Chief, Hematology Product Review Branch, DHCR, OBRR, CBER

STN BLA #: 125426/000/000 (original submission) and 125426/000/018 (resubmission; including new nonclinical data)

APPLICANT: Cangene, Corp., doing business as (DBA) Emergent Biosolutions, Winnipeg, MB, Canada (formerly 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 amendment 018 (resubmission) containing new nonclinical information

DATE: July 22, 2014

FINAL RECOMMENDATION:
Based on the nonclinical information included in amendment STN BLA#125426/0/18 and in the original BLA submission STN #A124426/0/0, this application is recommended for approval. The nonclinical data from both submissions support that IXINITY™ is reasonably safe for its intended use in the control and prevention of bleeding episodes, for peri-operative management, and for secondary, tertiary, or intermittent prophylaxis of bleeding episodes in adult and pediatric (12 years of age or older) patients with Hemophilia B. There are no recommendations at this time for additional nonclinical studies as either

post-marketing requirements, or post-marketing commitments. A labeling review for the package insert for the IXINITY product will be provided as an addendum to the file at the time of product approval.

EXECUTIVE SUMMARY:

The nonclinical data provided in the resubmission (STN BLA #125426/000/018) demonstrate that the modified manufacturing process for IXINITY™ (codename IB1001MC) results in a decrease in the immunogenicity of the final drug product. Specifically, decreases in both the incidence and titer of antibodies directed against host cell proteins from the Chinese Hamster Ovary cell line used to produce the drug substance were obtained in rabbits injected with IB1001MC, as compared to animals injected with IXINITY produced by the previous (original) manufacturing process (codename IB1001FC). Comparable exposures to the recombinant, human Factor IX, as measured by area under the Concentration versus Time (AUC) curve were demonstrated in a pharmacokinetics study in rats, after a single intravenous injection of either IB1001FC or IB1001MC. Taken together, the nonclinical data included in this resubmission can be used to successfully bridge the nonclinical safety profile of the IXINITY drug product and establish that IB1001MC produced by the modified manufacturing process results in decreased immunogenicity (and likely improved patient safety), with comparable drug exposure to the IB1001FC product previously used in the nonclinical testing (i.e., the data submitted in the original BLA, STN #125426/000). Additionally, in the resubmission the Applicant provided a risk assessment of the potential extractable and leachable components present in the IB1001 (b) (4) in response to the Complete Review letter for the original submission.

Reviewer comment: The nonclinical studies submitted in support of the original BLA submission were previously reviewed by Dr. M. Keith Wyatt in his review of the original STN BLA #125426/000, and are documented in his mid-cycle memorandum of September 17, 2012. No additional review of those prior studies will be performed. The "Executive Summary" from Dr. Wyatt's previous memorandum will be included as the nonclinical section of the Summary Basis of Regulatory Action at the time that IXINITY™ is approved.

A review of the nonclinical studies and the risk assessment submitted in amendment STN BLA #125426/000/018 is provided, below.

NONCLINICAL STUDY REVIEW:

1. Repeat-dose intravenous toxicology study of IB1001 recombinant Factor IX drug product in (b) (4) rats. Study #IB1001-PT-R-025.

Reviewer comment: This study was previously reviewed by Dr. M. Keith Wyatt, in his review of the original BLA submission STN BLA #125426/000 and is documented in his mid-cycle memorandum of September 17, 2012. It will not be re-reviewed as part of this addendum to the original BLA review, with the exception of noting that rats were dosed daily with IB1001FC by intravenous injection for 28 days with no remarkable clinical, hematologic, serum chemistry, or gross or histopathologic toxicities reported.

2. 24-hour evaluation of the plasma pharmacokinetics of Factor IX samples following a single intravenous dose to (b) (4) rats. Study #IB1001-PT-017 ((b) (4) study #21583).

Reviewer comment: This study was previously reviewed by Dr. M. Keith Wyatt, in his review of IND #13551, amendment 72, submitted Jun 26, 2013. Dr. Wyatt concluded that the data provided in this submission supported the comparability of the IB1001MC IXINITY™ drug product manufactured by the

modified process to the IB1001FC product previously used in the nonclinical toxicology testing program to support the original BLA. Although this study will not be re-reviewed here, portions of Dr. Wyatt's review have been abstracted and are presented, below.

"24-HOUR EVALUATION OF THE PLASMA PHARMACOKINETICS OF FACTOR IX SAMPLES FOLLOWING A SINGLE INTRAVENOUS DOSE TO (b) (4) RATS. (b) (4) . Study#, 21583. June 2013; GLP-compliant.

Purpose: To evaluate the plasma pharmacokinetics (PK) of "former" and "modified" versions of IB 1001 (rFIX).

Method: Fifteen male (b) (4) rats per group (weight range, 298 – 388 g) were implanted with jugular vein and carotid artery catheters and dosed by intravenous infusion with a single, nominal dose of 0.5 mg/kg of either the 'former' (Group 1; lot #F9005L1005, from source material lot #(b) (4)) or 'modified' IB 1001 (Group 2; lot #F9032L1212, from source material lot (b) (4)) product, using an automated drug infusion system. Blood samples were collected 2, 5, 15, 30, 45, 60 minutes and 2, 4, 6, 8 and 24 hours after completion of the infusion, and plasma was evaluated for human Factor IX levels using a commercially available (b) (4) kit ((b) (4)), by a sub-contractor laboratory. Statistical analysis for non-inferiority was performed, to demonstrate that the calculated PK parameters from the two groups (e.g., area-under-the curve, AUC) dosed with 'modified' or 'former' IB 1001 were not significantly different.

Results: One rat died pre-test during a patency examination of the catheters, but no rats administered either version of IB 1001 died during the study. Body weights were not changed significantly and clinical observations were not remarkable over the duration of the study.

Without adjusting for differences in the actual and target doses of IB 1001, the ratio of the geometric means for the AUC_{0-24} values from rats dosed with the 'former' and 'modified' versions of IB 1001 was 83%. This ratio is above the required 80% for the Sponsor's specified margin of non-inferiority; therefore the 'modified' version is not considered inferior to the 'former' version of IB 1001. However, the lower boundary of the one-sided 95% confidence interval (CI) for the ratio of the AUC_{0-24} geometric means between the 'former' and 'modified' versions was 78%; therefore, the lower CI boundary is below the specified margin of non-inferiority, and the 'modified' version cannot be considered bioequivalent to the 'former' version of IB 1001. Additional results from the Sponsor's non-inferiority analysis are presented in Table 1 (excerpted from the submission) that follows:

Table 1. Non-inferiority analysis of IB 1001 PK in rats (Table 6 in the submission)

Parameter	Original/Former Commercial Process IB1001 Results [N=15] (mean ± SD, Geometric Mean ± CV)	Polished/Modified Commercial Process IB1001 Results [N=15] (mean ± SD, Geometric Mean± CV)	Mean Ratio[a]	Lower Bound of One-Sided 95% Confidence Interval for the Ratio of Means[a] (Polished/Original)
α-phase half-life (hours)	1.55 ± 0.37; 1.51 ± 23.8%	1.38 ± 0.26; 1.36 ± 18.6%	0.90	0.79
β-phase half-life (hours)	5.50 ± 0.28; 5.50 ± 5.1%	5.34 ± 0.29; 5.34 ± 5.4%	0.97	0.94
Clearance (mL/hr)/10[6]	2.37×10^{-3} ± 2.66×10^{-4}; 2.35×10^{-3} ± 11.3%	2.85×10^{-3} ± 2.59×10^{-4}; 2.84×10^{-3} ± 9.1%	1.21	1.14
Mean residence time (hr)	5.50 ± 0.38; 5.49 ± 6.8%	5.40 ± 0.27; 5.40 ± 5.0%	0.98	0.95
Volume of distribution at steady state (mL/10[6])	$0.0001 \pm 2.58\times10^{-5}$; 0.0001 ± 24.2%	$0.0002 \pm 4.88\times10^{-5}$; 0.0002 ± 29.3%	1.52	1.28
C_{max} (ng/mL)	6476.95 ± 624.87; 6449.75 ± 9.6%	5765.18 ± 651.81; 5733.16 ± 11.3%	0.89	0.83
IVR (ng/mL per mg/kg)[b]	12953.9 ± 1249.74; 12899.5 ± 9.6%	11530.36 ± 1303.62; 11466.3 ± 11.3%	0.89	0.83
AUC_{0-inf} (ng-hr/mL)	21292.66 ± 1998.2; 21194.47 ± 9.4%	17697.08 ± 1610.1; 17628.49 ± 9.1%	0.83	0.78
AUC_{0-24} (ng-hr/mL)	20544.57 ± 1943.73; 20448.16 ± 9.5%	17109.45 ± 1559.89; 17042.94 ± 9.1%	0.83	0.78

a. Based on the one-sided confidence interval for the difference in the log means.
b. IVR is calculated based on the target nominal dose of 0.5 mg/kg.

To address the potential differences in PK comparability of 'modified' and 'former' IB 1001, the PK parameter data were re-evaluated (i.e. sensitivity analysis) after adjusting for the actual dose concentration of the administered test samples. Based on results of the dose analysis, the actual dose of the 'former' version of IB1001 administered to the rats in Group 1 was significantly (approximately 10%) greater than the dose of 'modified' IB 1001 administered to the Group 2 animals. The Sponsor states that this statistically significant difference in dose amounts accounts for the failure to show the non-inferiority of "modified" IB 1001. The results from the analysis of the actual IB 1001 dose concentrations administered to each group are presented in Table 2 (excerpted from the submission) that follows:

Table 2. Summary of dose solution concentration (Table 7 in the submission)

Group	Mean (SD)	P-value
Original/Former Commercial Process Product	0.487 ± 0.051 mg/mL	0.0006[a]
Polished/Modified Commercial Process Product	0.444 ± 0.025 mg/mL	

a. Two-sample t-test.

Based on the approximate 10% difference between the IB 1001 concentrations in the 'modified' and 'former' products, the Sponsor adjusted the dose amounts using the following equation (excerpted from the submission):

Adjusted [PK parameter]I = [PK parameter]i/[dose adjustment factor]

where the dose adjustment factor equals the actual dose concentration/target dose (0.4 mg/mL**)**

Reviewer comment: The results from the analysis of the Factor IX dose concentration showed that the administered 'actual' dose was within 11 to 22 percent of the 0.5 mg/kg target doses of both the 'modified' and 'former' version of IB 1001. The disparity between the target and actual doses may not be acceptable during a GLP compliant study where a difference no greater than 10% is allowed.
The Sponsor then conducted a sensitivity analysis to re-evaluate the PK parameters after adjustment for the IB 1001 dose differences. This analysis showed that the lower CI boundary of the ratio of the geometric mean AUC values from the 'former' and 'modified' versions of IB 1001 was 85%, which is above the 80% required to demonstrate the non-inferiority of the "modified" version of IB1001.
Additional results from the sensitivity analysis are presented in Table 3 (excerpted from the submission) that follows:

Table 3. Summary of sensitivity analysis-dose adjustment (Table 8 in the submission)

Parameter	Original/Former Commercial Process IB1001 Results [N=15] -dose corrected (mean ± SD, Geometric Mean ± CV)	Polished/Modified Commercial Process IB1001 Results [N=15] -dose corrected (mean ± SD, Geometric Mean ± CV)	Mean Ratio -dose corrected	Lower Bound of One-Sided 95% Confidence Interval for the Ratio of Means[a] (Polished/Original) -dose corrected
Clearance (mL/hr)/10^6	$1.96x10^{-5} \pm 3.07x10^{-6}$ $1.94x10^{-5} \pm 15.7\%$	$2.58x10^{-5} \pm 3.25x10^{-6}$ $2.56x10^{-5} \pm 12.6\%$	1.32	1.21
Volume of distribution at steady state (mL/10^6)	$8.85x10^{-5} \pm 2.35x10^{-5}$, $8.64x10^{-5} \pm 26.6\%$	$1.51x10^{-4} \pm 4.62x10^{-5}$, $1.43x10^{-4} \pm 30.5\%$	1.66	1.38
C_{max} (ng/mL)	5387.02 ± 909.90, 5321.28 ±16.9%	5204.19 ± 659.50, 5168.77 ± 12.7%	0.97	0.89
IVR (ng/mL per mg/kg)	10408.38±1319.007, 10337.54±12.7%	10774.03±1819.79, 10642.56±16.9%	0.97	0.89
AUC_{0-inf} (ng-hr/mL)	17634.04 ± 2366.64, 17486.21± 13.4%	15950.68 ±1406.59, 15893.07 ± 8.8%	0.91	0.85
AUC_{0-24} (ng-hr/mL per mg/mL)	42542.66 ± 5785.40; 42176.21 ± 13.6%	38552.59 ± 3414.97; 38412.91 ± 8.9%	0.91	0.85

a. Based on the one-sided confidence interval for the difference in the log means.

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Reviewer comment: The excerpt from Dr. Wyatt's review ends here.

The Applicant's reanalysis of the data after correction for the differences in protein concentration was independently confirmed by the review team for the original BLA submission (not shown; documented in Dr. Wyatt's review of IND 13551, amendment 72), who concluded that IB1001MC did achieve comparable exposures, as shown by the corrected AUC values to the previous IB1001MC product. These data can be used to bridge the nonclinical safety profile of IB1001FC to the expected safety profile of IXINITY™ produced by the modified manufacturing process, and suggest that no adjustment of dosing will be needed for the IB1001MC drug product.

3. Assessment of CHO Cell Protein Immunogenicity Response in (b) (4) Rabbits after 9½-weeks of Intravenous Administration (non-GLP). Study #1914-008.

Purpose: To compare the immunogenicity of residual CHO host cell proteins in IB1001 IXINITY™ drug product manufactured by the former commercial manufacturing process (IB1001FC; original BLA submission) and the modified commercial manufacturing process (IB1001MC, resubmission) after repeat dosing in (b) (4) rabbits.

Conducting laboratory and location: (b) (4)

Date of study initiation: Jun 28, 2013 (in-life phase 7/16 – 9/23/2013); final study report signed Dec 6, 2013

GLP compliance: No; however, this study had inspections and data/report audits performed by the Quality Assurance Unit at (b) (4), and a signed QA statement was provided.

Drug, lot#, and % purity: recombinant human Factor IX, product codes IB1001FC [Former Commercial (FC) manufacturing process; GMP#31], lot #F9030H1205; 97% pure ((b) (4)), 100% pure ((b) (4)); and IB1001MC [Modified Commercial (MC) manufacturing process; GMP#47], lot #F9034H1302; 96% pure (b) (4)), 98% pure (b) (4)), 99% pure ((b) (4)), 100% pure ((b) (4))

Methods
Doses: 0.5 mg/kg/dose, for both groups

Frequency of dosing: Twice weekly, x 9½ weeks (total of 18 doses)

Route of administration: Intravenous bolus injection (marginal ear vein)

Dose volume: 0.4 mL/kg (FC product, dose concentration 1.24 mg/mL); 0.42 mL/kg (MC product, dose concentration 1.20 mg/mL)

Formulation/Vehicle: lyophilized; dilute with Sterile Water for Injection (sWFI)

Species/Strain: Rabbit ((b) (4) strain

Number/Sex/Group: 12/sex/group

Age: approximately 7 weeks of age at initiation of dosing

Weight: 2.65 – 3.16 kg (males); 2.57 – 3.43 kg (females) at randomization

Observations and Results

Mortality

Rabbits were observed twice daily, approximately 6 hours apart for mortality, morbidity, or injury. All animals survived until terminal sacrifice on Study Day 70.

Clinical Signs

All study animals were examined by the staff veterinarian prior to study initiation on SD-8, and weekly during the study. All rabbits were also examined for effects of IB1001FC or IB1001MC on respiratory and circulatory functions, autonomic effects (e.g. salivation), and effects on the nervous system (e.g. tremors, convulsions, reactivity to handling, unusual behavior) following dosing. No abnormalities in physical or behavioral evaluations were noted in any animals on study. Daily clinical observations included occasional reports of mild bruising and discoloration of the skin and/or hair at the ear vein injection sites in 10/24 rabbits treated with IB1001FC, and in 18/24 animals dosed with IB1001MC. These findings are related to repeated intravenous injections, and are unrelated to toxicity of IB1001 manufactured by either the former or modified commercial processes.

Body Weights and Feed Consumption

Body weights and food consumption were measured and recorded once weekly beginning on Study Day (SD) -8. There were no remarkable differences in mean body weights between the groups of male or female rabbits treated with IB1001FC and IB1001MC at any time point during the study. Occasional minor differences in mean weekly feed consumption were observed between the groups of rabbits treated with IB1001FC and IB1001MC; both male and female rabbits in the IB1001FC group showed decreases between 2 and 7 g/day in feed consumption beginning Study Week 1 for male rabbits, and Study Week 2 for female animals, as compared to the corresponding sexes in the IB1001MC dose group.

Reviewer comment: The toxicologic relevance of the decreased food consumption by both male and female rabbits in the IB1001FC dose group is unknown. No differences in mean body weights or body weight gain were reported over the duration of the study; therefore, the findings of lower body weights in the IB1001FC treated rabbits are unlikely to be biologically significant.

Clinical Pathology

Peripheral blood samples for hematology and coagulation profile assessments were collected from all animals prior to terminal necropsy, without fasting or withdrawal of access to water overnight. Statistically significant, 23% decreases in both total leukocytes and neutrophil counts and 25% decreases

in total lymphocyte counts were reported in male rabbits dosed with IB1001MC drug product, as compared to the male animals dosed with IB1001FC produced by the former commercial manufacturing process. Slight, but statistically significant increases in hematocrit (4%) and hemoglobin concentration (5%) were also reported in female rabbits dosed with IB1001MC compared to the females dosed with the IB1001FC product. However, no vehicle control group was included in this study and no baseline samples were obtained for these animals prior to treatment, for comparison. Additionally, the effects were not observed in animals of both sexes, therefore these findings are not considered toxicologically meaningful.

There were no remarkable differences in coagulation profiles (PT, aPTT) between rabbits dosed with IB1001FC or IB1001MC, and all values were within the historical control range for the testing laboratory. At necropsy, there were no toxicologically meaningful differences in mean organ weights or macroscopic pathology findings between the groups of rabbits dosed with IB1001FC or IB1001MC. Incidental macroscopic findings included absent left thyroid and parathyroid glands in one female rabbit treated with IB1001FC (animal #1502), a missing portion of the uterine horn in a second female rabbit (animal #1509) in this dose group, and a cyst on the right kidney in one female rabbit dosed with IB1001MC (animal #2509). No histopathologic evaluation was performed for this study.

Reviewer comment: The above macroscopic pathology findings are typically developmental anomalies, and were within historical limits for control animals at the contracting laboratory. Alternatively, the cyst on the kidney could be an acquired pathology; however, it was only seen in one animal and therefore is of little toxicologic significance.

Toxicokinetics

Blood samples for evaluation of plasma levels of IB1001 were obtained from a total of 3 rabbits pre-treatment, and at 1 and 12 hours after dosing on SD 1, 29, and 57, and levels of IB1001 were quantitated using a commercially available, (b) (4)) that specifically detects human Factor IX. Prior to injection, all rabbits at the SD 1 and 29 time points had IB1001 levels below the level of quantitation of the assay; at SD 57, 2/3 rabbits sampled had undetectable IB1001 levels, while a low level was detected pre-treatment in the third rabbit (445 ng/mL, animal #1504F). Peak IB1001 levels were reported 1 hour post-dosing for all time points, and ranged between 4815 and 9590 ng/mL. There were no statistically significant differences in the mean plasma IB1001 levels over time, indicating that neither accumulation nor accelerated clearance of the drug product was occurring after repeat administration. Antibodies specifically directed against IB1001 or human Factor IX were not measured in this study.

Immunogenicity Analysis

Serum samples for immunogenicity assessment were collected from all rabbits prior to dosing on Study Days 1, 29, and 57 and assayed for the presence of anti-CHO host cell protein antibodies using a previously validated (b) (4). Positive anti-CHO antibody development (i.e. seroconversion) was defined as a positive (b) (4) result after at least a 4-fold dilution of the serum sample from the IB1001-treated rabbits into control rabbit serum.

At SD 29, there was no seroconversion detected in the rabbits treated with IB1001MC, manufactured using the modified commercial process. By contrast, 19 of 24 rabbits dosed with IB1001FC produced by the former commercial process had detectable anti-CHO host cell protein antibodies present ($p < 0.0001$, Fisher's Exact Test). At SD 57, the incidence of seroconversion in the group treated with IB1001FC had increased to 23/24 rabbits, with anti-CHO antibody titers ranging from 1170 to 32,390. Only a single rabbit in the group dosed with IB1001MC developed a positive anti-CHO host cell protein antibody response, and with a titer or 117. The results of this study are summarized in Table 4, below:

Table 4. Summary of Anti-CHO Host Cell Protein Antibody Development in Rabbits after Repeated Injection of IB1001 Produced by the Former (IB1001FC) or Modified (IB1001MC) Commercial Manufacturing Processes

Summary of Results	Study Day 29		Study Day 57	
	IB1001FC	IB1001MC	IB1001FC	IB1001MC
Incidence of Anti-CHO Ab Positive Rabbits	19/24	0/24	23/24	1/24[a]
Percentage of Animals Anti-CHO Ab Positive	79	0	96	4
95% CI[b]	N/A[b]	N/A	[0.788, 0.999]	[0.001. 0.211]
Mean Anti-CHO Ab Titer, ± S.D.	3137 ± 2939	N/A	15616 ± 12014	117 (N/A)
Median Anti-CHO Ab Titer (Range)	3235 (0, 7553)	N/A	14809 (1170, 32390)	117 (117, 117)
95 % CI	[680, 5594]	N/A	[5572, 25660]	N/A

[a] $p < 0.0001$, Fisher's Exact test
[b] CI = confidence interval; N/A = not available

STUDY CONCLUSION:

No remarkable toxicities were reported in rabbits after intravenous dosing twice weekly for 18 doses (9.5 weeks) with IXINITY™ manufactured using either the former (IB1001FC) or modified (IB1001MC) commercial manufacturing processes. At the end of the treatment period at SD57, there was a marked, statistically significant decrease in the incidence of immunogenicity to the CHO host cell proteins in rabbits dosed with IB1001MC, as compared to the group dosed with IB1001FC. These data suggest that IXINITY™ manufactured using the modified commercial process will have significantly reduced potential for anti-CHO host cell protein antibody development in patients with Hemophilia B receiving the product for the proposed indications of treatment or prophylaxis of bleeding, with a resulting improvement in the product safety.

RISK ASSESSMENT OF EXRACTABLE AND LEACHABLE COMPONENTS FROM DIRECT CONTACT EQUIPMENT AND MATERIALS USED IN THE IXINITY™ DRUG SUBSTANCE MANUFACTURING PROCESS (Applicant's response to FDA Comment #13 in the Complete Review letter of Feb 1, 2013)

The following two reports were included in the resubmission (STN BLA #125426/00/018), to address FDA's request for this information:

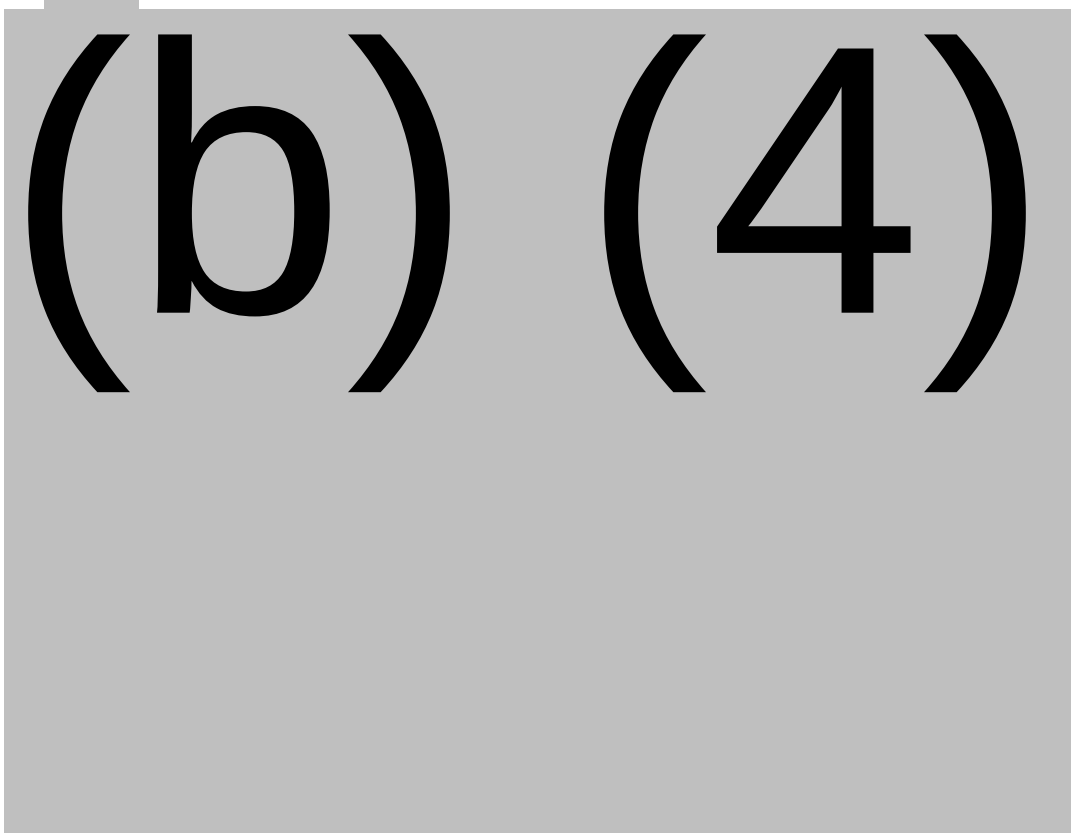
1. Extractables and leachables assessment for IB1001 Drug Substance manufacturing process constructs. Report #BAR-725-FIX-13-007-PR-v1.
2. Risk assessment report for Project 366 (F90) Extractables/Leachables. Report #F90-PRA-15.

These two reports provided a comprehensive risk assessment of potential leachable compounds from the components used in the manufacture of IXINITY™, specifically of those direct contact materials and equipment used in the IB1001 Drug Substance (DS) manufacturing process. Initially, high risk constructs

in the drug substance manufacturing process were identified, and extractable components were obtained from these constructs under conditions that exceeded the conditions of use (e.g. solvent extraction) and quantitated. For those components identified as potentially high risk, worst-case concentrations were calculated based on these quantitation results, available literature or other manufacturer's available data, scaled for the actual conditions of use in the IB1001 DS process. These concentrations were then used to estimate maximum daily patient exposures, based on the recommended maximal dose of the IXINITY drug product (i.e., for peri-operative management of bleeding, approximately 70 IU/kg for a 60 kg patient).

Ten constructs were identified as high risk for extractable or leachable components entering the IB1001 DS, and assigned a risk category based on the availability of safety information available from the vendor or the open literature, or whether additional testing is required. A list of the components identified as high risk, as well as a description of the risk categories is provided in Table 5 (excerpted from the Applicant's report), below.

(b) (4)



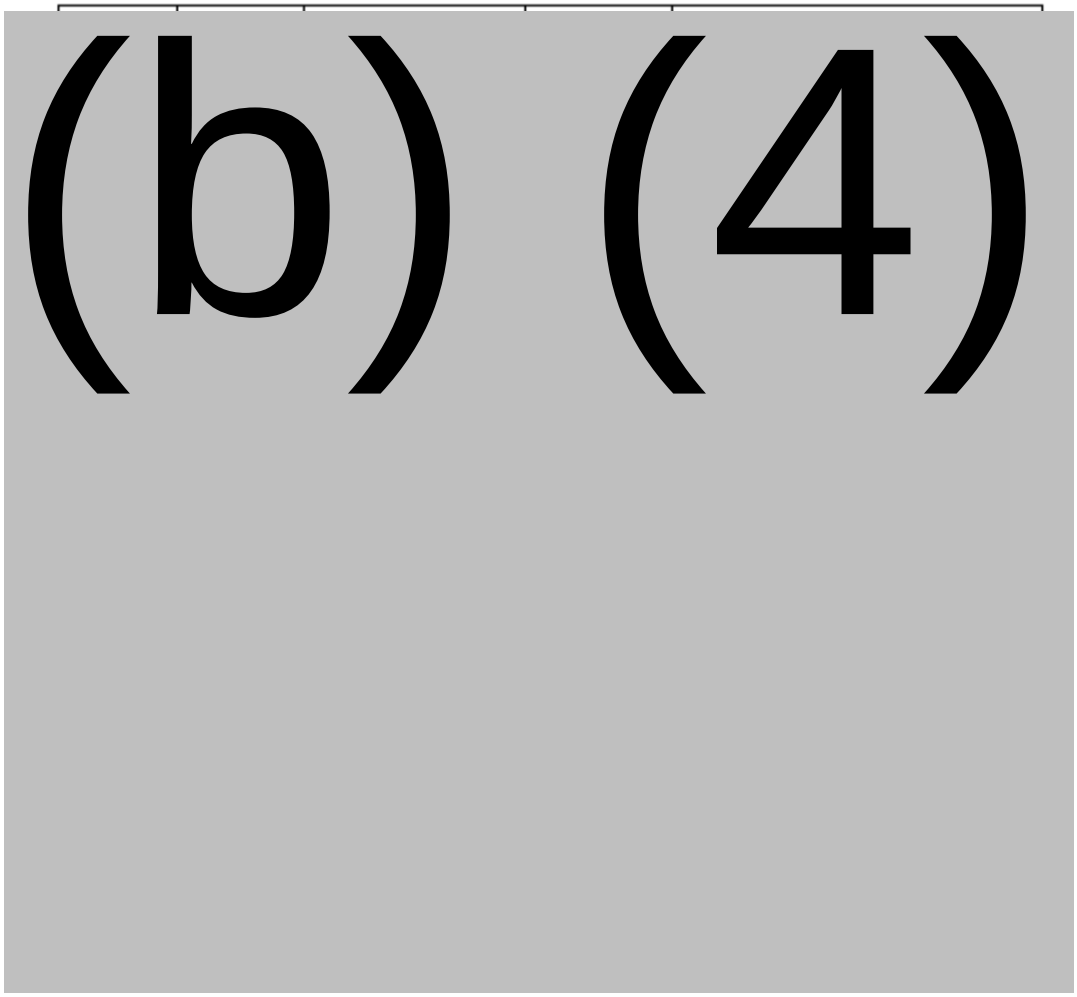
All Category I manufacturing components ((b) (4)) were adequately qualified for safety of potential extractable and leachable materials by available information in the literature, and by the vendor/manufacturer's certificates confirming compliance with either USP Class VI criteria or 21 CFR 177.2600. Additionally, since the concern was related to (b) (4) that comes into contact with these parts (b) (4)), the Applicant provided information from the literature that confirms that any extracted compounds resulting from (b) (4) would be sufficiently diluted by the (b) (4) step. The (b) (4)

3 pages determined to
be not releasable:(b)(4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)



STUDY CONCLUSION:
The Applicant has provided extensive identification and qualification of the safety of the extractable and potential leachable substances from the components used in the IB1001 DS manufacturing process. Additionally, the safety of these extractable compounds can be considered adequately qualified because several lots of the IB1001 DS were used in the nonclinical toxicology testing, at daily doses of IB1001 exceeding the recommended clinical dose by up to 10-fold (e.g. Study # IB1001-PT-R-025, 28-day repeat-dose toxicology study in (b) (4) rats). The risk of the presence of these compounds to patients with Hemophilia B receiving intravenous doses of IXINITY™ for treatment or prophylaxis of bleeding at the levels identified is considered minimal, and acceptable considering the benefit of Factor IX replacement therapy in this population.