



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Building 71, G112
Silver Spring, MD 20993-0002

To: DATS: 608607

STN BLA 125591/0
Antihemophilic Factor (Recombinant), rVIII-SingleChain

From: LCDR Donald Ertel, Regulatory Officer, OCBQ / DMPQ / MRB1

Through: Carolyn Renshaw, Branch Chief, OCBQ / DMPQ / MRB1

CC LT Thomas Maruna, RPM, OBRR/DBCD
Alexey Khrenov, Ph.D., Chair, OBRR/DHRR/LH

Subject: DMPQ Primary Review for Original Biologics License Application filed per 21 CFR 601.2 for Antihemophilic Factor (Recombinant), VIII SingleChain indicated for the treatment and prophylaxis of patients with hemophilia A (congenital Factor VIII deficiency)

Applicant: CSL Behring Recombinant Facility Ag (CSLBRF) (License #2009)

Facility (b) (4)

2. CSL Behring GmbH (CSLB) FEI # 3003098680 - Emil-von-Behring-Strasse
76 D-35041 Marburg Germany

ADD: 28 May 2016

Conclusion and Recommendation

I recommend approval of this submission. The qualification and validation activities, as related to facility, equipment, and container closure appear adequate for the manufacture of antihemophilic Factor (Recombinant), VIII SingleChain. This is my final review memo for this submission; there will be no subsequent addendum reviews. I reviewed DMF (b) (4) (in Feb 2016 as part of review for rIX-FP, BLA STN 125582/0) for the Sterile Water for Injection, which is co-packaged with the product; the review is attached to this file. (My DMF review dated 18 Feb 2016 is on file with CDER DCC)

Review Memo Format and Table of Contents

I have provided a summary of information provided in the submission that is under DMPQ purview as outlined in SOPP 8401.4: In general, my Review Assessment / Comments are provided at the end of review sections in a double lined box. Any information requests (IRs) related to review will be included in these boxes in bolded text. A summary of the firm's response to that IR will immediately follow in italicized text or in a subsequent Amendment Review memo. My assessment of the response will immediately follow in a double lined box.

The table of contents of this review is as follows (major sections numbered, subsections lettered):

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1. Amendments related to Review

➤ 125591/0.9 received 19 Nov 2015 to Information Request on 05 Nov 2015

2. Regulatory History

The agency received the BLA in eCTD format on 29 May 2015. I was assigned as a CMC reviewer on 04 June 2015. The application was appropriately filed per 21 CFR 601.2

One Inspection Waiver was submitted and approved for this submission for the CSL Behring facility (approved 12 Nov 2015). CBER performed a Pre-license inspection at the (b) (4)

CLSB RF recently submitted a BLA STN 125582/0 for rIX-FP (another recombinant coagulant factor product), and was approved on 04 Mar 2016. I performed the Facility and Equipment CMC review for the submission, as well as lead for the PLI at the CSL Behring Marburg facility.

CSLB manufactures rVIII-SingleChain and rIX-FP in common production areas in a campaign mode. For both products, three CSLB facilities in Marburg, Germany are employed for the same stages of the manufacturing process as follows:

- Building (b) (4) Manufacture of Drug Substance (DS), Manufacture of the Final Product, Pretreatment of Equipment
- Building (b) (4) for Filling and Lyophilization of the Final Product
- Building (b) (4) for Packaging and Labeling of the Final Product.

Consequently, there is a significant overlap between the facility areas, utilities, and systems for these two products.

According to their amendment, with the exception (b) (4) (b) (4), CSLB shares the major equipment for (b) (4) (b) (4) of the final products between the manufacture of rVIII-SingleChain and rIX-FP. For Manufacture of DS in (b) (4), shared equipment is limited to equipment (b) (4) while all other equipment with direct product contact (e.g. (b) (4)) is either dedicated or single use.

The commonality between the two submissions is as follows:

(b) (4)

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(b) (4)

(b) (4)

Review Comment/ Assessment: Because much of the data on the same facilities, and associated utilities, and equipment was recently scrutinized in STN 125582/0, the following items appear to be the critical items to be evaluated as part of this review:

- | | |
|----|---|
| 1. | Process Validation |
| 2. | Product Contact Equipment Cleaning Validation or Evaluation (b) (4) |
| 3. | Stability Studies |
| 4. | Qualification of Lyophilizer (b) (4) |
| 5. | Stability |

3. Environmental Assessment

CSLBRF is claiming an exemption from the requirement for preparing an environmental assessment for this BLA for rVIII-SingleChain, based upon 21 CFR 25.31(c) which allows a categorical exclusion for an action on an application for marketing approval, for marketing a biologic product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

rVIII-SingleChain is a single-chain recombinant Factor VIII produced in CHO cells. It is a construct where most of the B-domain occurring in wildtype, full-length FVIII and four amino acids of the adjacent acidic a3 domain were removed (amino acids 765 to 1652 of full-length FVIII). The newly formed linkage of the heavy and light chain of FVIII introduces a new N-glycosylation site. As the (b) (4) (b) (4) rVIII-SingleChain is expressed as a single-chain FVIII molecule. After activation by thrombin and removal of the (b) (4) B- and a3-domain, the activated rFVIII (rFVIIIa) molecule formed has an amino acid sequence identical to FVIIIa formed from endogenous, full length, FVIII.

<p><u>Review Assessment / Comments:</u> To CSL's knowledge, no extraordinary circumstances exist. I am in agreement with the CE.</p>
--

4. Product and Overall Process

CSL627 (internal company product code) is a preservative-free, lyophilized formulation presented in five dosage strengths of 250, 500, 1000, 2000 and 3000 IU. Each individual dosage size is presented in single-use glass vials of 6 mL (250, 500 and 1000 IU) or 10 mL (2000 and 3000 IU) nominal capacity. The active pharmaceutical ingredient, recombinant, single-chain coagulation factor VIII (rVIII-SingleChain) is formulated in a (b) (4) containing (b) (4). CSL627 is intended for intravenous injection.

For use, the lyophilized CSL627 is reconstituted using sterile WFI (referenced to DMF (b) (4)) and a needleless Mix2vial™ transfer device, giving volumes of 2.5 mL (for 250, 500 and 1000 IU) and 5 mL (for 2000 and 3000 IU). Instructions for the reconstitution of CSL627 are supplied with the product.

Manufacture of rVIII-Single Chain starts at (b) (4) is shipped to CSL Behring, Germany (CSLB)

for further purification up to the (b) (4) The major steps of the process are as follows:

(b) (4)

CSL Behring	(b) (4)	(b) (4)
	(b) (4)	
	(b) (4)	
	(b) (4)	Formulation and Sterile Filtration
	(b) (4)	Filling
	(b) (4)	Lyophilization
	(b) (4)	Capping and Crimping
(b) (4)	Labelling and Packaging	

Batch and Scale

(b) (4)

5. Overall Manufacturing and Testing Facilities

The facilities involved in the manufacture and testing of rVIII-SingleChain (CSL627) are listed below along with a short description of their manufacturing responsibilities and an indication if an inspection was performed.

Manufacturing / testing activity	Facility	Comments
		Inspection Waived
Transfer Device Mix2Vial®	Manufactured by Medimop; Supplied by CSLB	510K Cleared device #K031861 No inspection or waiver
Stability testing and storage of samples	CSLB	Inspection Waived
Records or quality assurance functions with no testing		
Storage of drug substance and drug product		

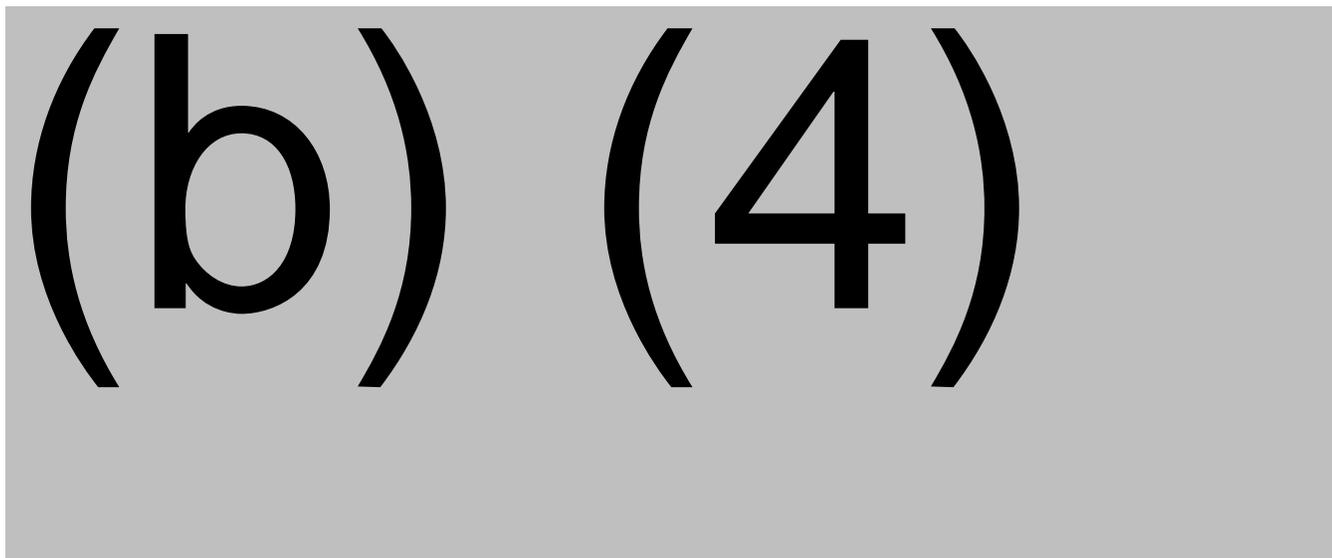
Testing is performed as follows:

(b) (4)

Company	<div style="font-size: 48pt; font-weight: bold;">(b) (4)</div>															
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px;">(b) (4) Activity (FVIII activity) (Chromogenic activity) (b) (4)</td> <td rowspan="14" style="width: 50%; text-align: center; vertical-align: middle;">DP Release</td> </tr> <tr> <td style="padding: 2px;">(b) (4)</td> </tr> <tr> <td style="padding: 2px;">PS-80</td> </tr> <tr> <td style="padding: 2px;">Protein concentration</td> </tr> <tr> <td style="padding: 2px;">Practicability and organoleptic properties</td> </tr> <tr> <td style="padding: 2px;">(b) (4)</td> </tr> <tr> <td style="padding: 2px;">Residual moisture</td> </tr> <tr> <td style="padding: 2px;">Sodium</td> </tr> <tr> <td style="padding: 2px;">Calcium</td> </tr> <tr> <td style="padding: 2px;">Sucrose</td> </tr> <tr> <td style="padding: 2px;">Histidine</td> </tr> <tr> <td style="padding: 2px;">Sterility</td> </tr> <tr> <td style="padding: 2px;">Particulate matter</td> </tr> <tr> <td style="padding: 2px;">(b) (4)</td> </tr> </table>			(b) (4) Activity (FVIII activity) (Chromogenic activity) (b) (4)	DP Release	(b) (4)	PS-80	Protein concentration	Practicability and organoleptic properties	(b) (4)	Residual moisture	Sodium	Calcium	Sucrose	Histidine	Sterility	Particulate matter
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Histidine																
Sterility																
Particulate matter																
(b) (4)																

6. Processing Equipment Overview

The main production equipment used for Drug Substance production of rVIII in Bldg. (b) (4) at CSL Marburg are:



(b) (4)

7. Equipment Cleaning Validation

CSLBRF reports that, with exception of (b) (4) (b) (4), all product contact equipment and parts are dedicated to rVIII or single-use. The main equipment that was not qualified in studies for rIX-FP is as follows:

(b) (4)

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(b) (4)

8. Lyophilizer Qualification

With a surface of (b) (4) lyophilizers (b) (4) are identical and installed in (b) (4) rooms on the (b) (4) floor of building (b) (4). The (b) (4) with the partially closed vials are (b) (4)

(b) (4)

(b) (4)

2 Pages have been determined to be not releasable: (b)(4)

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

Performance Qualification Studies:

In addition to the PPQ outlined in Section 10 of this memo, CSLB performed separate lyophilization validation runs to demonstrate the consistency of lyophilization operations for each rVIII-SingleChain DP presentation. The batches used for these lyophilization validation studies were manufactured using the same process and container closures as that used for the PPQ batches. The results are summarized in the attached Lyophilization Validation of rVIII-SingleChain / CSL627 reports:

2 Pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

9. Process Validation

Based on the results for IPCs, IPACs and the evaluation of process parameters, CSLB validated the production process at full scale according to their current commercial scale manufacturing

and process descriptions. Ancillary validation studies were performed for critical mixing steps, the (b) (4), cumulative hold times, buffer preparation, the filling and lyophilization process, as well as for a (b) (4)

The validation batches for BDI at (b) (4) were as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

4 Pages have been determined to be not releasable: (b)(4)

(b) (4)

The Acceptance Criteria for Final Product (for all doses except where specified) was based on the Lot Release Specification:

Test parameter	Test code	Specification
Sterility	Q-01-003/ Q-25-002	Sterile, according to requirement of (b) (4) /CFR ^{(b) (4)}
Dissolution time	Q-04-003	≤ 5 min
Appearance of the lyo cake		White or slightly yellow powder (b) (4)
Appearance of the solution		Almost colorless, clear to slightly opalescent solution
FVIII:C activity	Q-10-006	(b) (4) IU/mL (250IU) (b) (4) IU/mL (500IU) (b) (4) IU/mL (1000, 2000 IU) (b) (4) IU/mL (5000 IU)
(b) (4)	Q-16-023	(b) (4)
(b) (4)	Q-16-021	(b) (4)
Sodium	Q-16-018	(b) (4)
Calcium	Q-16-017	(b) (4)
Sucrose	Q-16-086	(b) (4)
Protein content	Q-16-411	(b) (4)
Histidine	Q-16-081	(b) (4)
Polysorbate 80	Q-16-408	(b) (4)
(b) (4)	Q-16-410	(b) (4)
Residual moisture	Q-16-345	(b) (4)
Particulate contamination – (b) (4)	Q-16-112	(b) (4)
(b) (4)	Q-11-031	Specification according to (b) (4).
(b) (4) FVIII:C activity	Q-10-006S6	(b) (4)
Toxicity	Q-21-101	Specification according to (b) (4)
Endotoxins	Q-24-314	(b) (4)
Protein composition (b) (4)	Q-42-046	(b) (4)

Process Validation for the Filling process

- rVIII-SingleChain 250 IU, PV-808-024-01
- rVIII-SingleChain 500 IU, PV-808-025-01
- rVIII-SingleChain 1000 IU, PV-808-026-01
- rVIII-SingleChain 2000 IU, PV-808-027-01
- rVIII-SingleChain 3000 IU, PV-808-028-01

CSLBRF conducted these studies to provide evidence that the aseptic filling process performed on the ^{(b) (4)} floor of building (b) (4) consistently and reproducibly delivers a homogeneous DP meeting its pre-defined acceptance criteria and quality attributes. Furthermore the hold times for final bulk, (b) (4) were validated within these studies.

The following objectives are covered within this validation study:

(b) (4)

It was shown that the filled units after lyophilization were homogenous from the start to the end of the filling process with respect to (b) (4). Furthermore, no negative effect of the cumulated hold times on CQAs of the Drug Product (lyophilized final product) was detected. Testing of the DP was performed according to Quality Control Procedure Q-808G.

- For 250 IU, three validation runs were performed. Two deviations occurred during execution, no impact to filling validation.
- For 500 IU, three validation runs were performed. no deviations reported.
- For 1000 IU, three validation runs were performed. One deviation reported, no impact to filling validation.
- For 2000 IU, three validation runs were performed. Three deviations reported, no impact to filling validation.
- For 3000 IU, three validation runs were performed. Two deviations reported, no impact to filling validation.

Review Assessment/ Comments: Acceptance criteria correlate with specification. (b) (4) excursions were reported. No objectionable findings noted.

a. Hold Times

CSLBRF validated hold times from final bulk to the (b) (4) DP in production scale. The three validation batches for each presentation were manufactured at the worst-case of the defined limits and were cumulative in nature. The rVIII-SingleChain final bulk (b) (4) can be stored for (b) (4)

[Redacted]

validated. Data from the study was presented in the submission.

b. (b) (4) Studies

(b) (4)

[Redacted]

[Redacted]

[Redacted]

c. Mixing Studies

(b) (4)

[Redacted]

d. Media Simulations

CSLB performed a comprehensive Aseptic Processing Simulation study to include multiple vials, stoppers, (b) (4) filling Lines, and all Lyophilizers. CSLBRF determined that the Final Bulk can be stored at (b) (4) Stability data supporting this holding time was generated as part of PPQ. This time period encompasses the total time covering the (b) (4) The breakdown of hold times within these individual steps is as follows:

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

(b) (4)

[Redacted]

[Redacted]

4 Pages have been determined to be not releasable: (b)(4)

(b) (4)

[Redacted]

[Redacted]

Requalification

CSLB reports that each individual lyophilizer is required to be covered in media fill runs at least every (b) (4) and at least (b) (4) per financial year (time period of re-validation plan), and the following requalifications requirements (matrix):

(b) (4)

Review Assessment / Comments: The Aseptic process validation appears adequate, a minimum of three run were executed with the inclusion of each presentation across multiple shifts. The media fill runs were carried out with at least the equivalent maximum [target] batch size made on the processing line with at least (b) (4) vials for production sizes greater than (b) (4) vials. Environmental monitoring was performed during runs with acceptance criteria meeting acceptable room classification requirements. Relevant documents are referenced in the submission I Media Simulation recommendations in Guidance: Sterile Drug Products Produced by Aseptic Processing- Current Good Manufacturing Practice appears to have been met. No objectionable findings noted.

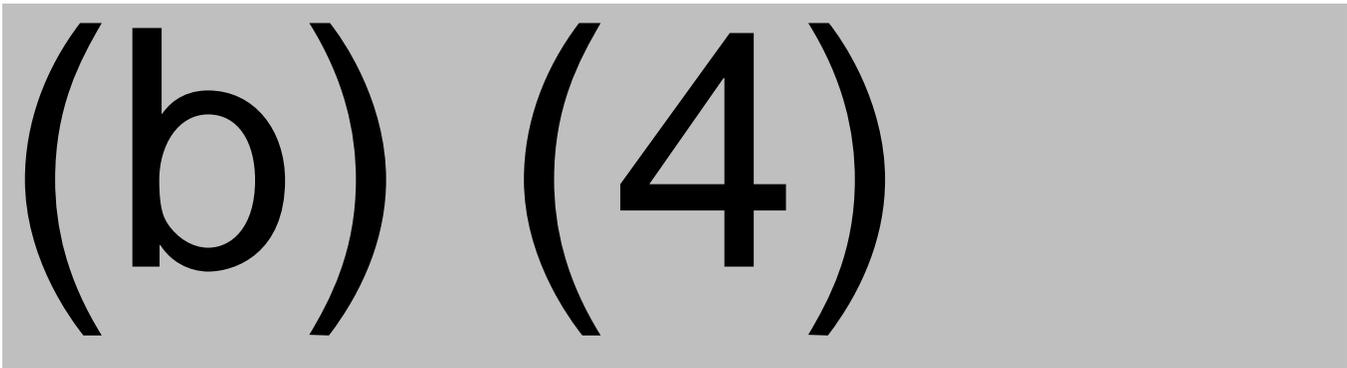
e. Filling (Drug Product)

Process Validation for the Filling process

- rVIII-SingleChain 250 IU, PV-808-024-01
- rVIII-SingleChain 500 IU, PV-808-025-01
- rVIII-SingleChain 1000 IU, PV-808-026-01
- rVIII-SingleChain 2000 IU, PV-808-027-01
- rVIII-SingleChain 3000 IU, PV-808-028-01

CSLB conducted these studies to provide evidence that the aseptic filling process performed on the ^{(b) (4)} floor of building ^{(b) (4)} consistently and reproducibly delivers a homogeneous DP meeting its pre-defined acceptance criteria and quality attributes. Furthermore the hold times for final bulk, ^{(b) (4)} were validated within these studies.

The following objectives are covered within this validation study:



It was shown that the filled units after lyophilization were homogenous from the start to the end of the filling process with respect to ^{(b) (4)}. Furthermore, no negative effect of the cumulated hold times on CQAs of the Drug Product (lyophilized final product) was detected. Testing of the DP was performed according to Quality Control Procedure Q-808G.

- For 250 IU, three validation runs were performed. Two deviations occurred during execution, no impact to filling validation.
- For 500 IU, three validation runs were performed. no deviations reported.
- For 1000 IU, three validation runs were performed. One deviation reported, no impact to filling validation.
- For 2000 IU, three validation runs were performed. Three deviations reported, no impact to filling validation.
- For 3000 IU, three validation runs were performed. Two deviations reported, no impact to filling validation.

Review Assessment/ Comments: Acceptance criteria correlate with specification. No objectionable findings noted.

3 Pages have been determined to be not releasable: (b)(4)

13. Container Closure

The container/closure system is (b) (4)

CSLB provided stability data to demonstrate that the container closure system is suitable for the storage and reconstitution of rVIII. The rVIII container closure system (primary packaging material) is as follows:

Item (#)	Specifications	Description
Container 6 mL (b) (4) 10ml (b) (4)	Type	Vial
	Material of construction	(b) (4) glass
	Compliance	(b) (4)
	Color	Colorless
	Nominal capacity	6 mL: 250 IU, 500 IU, 1000 IU 10 mL: 2000 & 3000 IU
Stopper (b) (4)	Type	Lyophilization stopper
	Material of construction	Bromobutyl rubber
	Compliance	(b) (4)
	Color	Grey
Overseal (Cap)	Type	(b) (4) combi cap
	Material of construction	Aluminum / Polypropylene
	Color	250 IU: green striped / orange (b) (4) 500 IU: green striped / blue (b) (4) 1000 IU: green striped / green (b) (4) 2000 IU: green striped / purple (b) (4) 3000 IU: green striped / yellow (b) (4)

With the exception of the color of the overseals, the container closure system is identical for the presentations of 250, 500, and 1000 IU, which are all filled in vials of 6 mL volume. The 2000 & 3000 IU fill size uses a 10 mL vial to allow for reconstitution with 5 mL WFI, instead of 2.5 mL for the other fill sizes.

CSLB reports that the containers are single use vials made of colorless, Tubular, (b) (4) glass meeting the (b) (4) requirements for parenteral administration in accordance with section (b) (4)

The vials are closed with (b) (4) bromobutyl rubber stoppers that comply with (b) (4) requirements of (b) (4) and the comparable requirements of (b) (4). The formulation of the stopper was not manufactured with natural rubber latex.

The stoppers are secured by combination caps consisting of an aluminum crimp cap with a concentric hole and an integrated polypropylene plastic disc. The crimp caps meet international standards for dimensional criteria.

The packaging material is accompanied by the vendor's documentation, which is controlled for each shipment. The procedures reflect current compendia requirements and the relevant national and international standards (DIN, EN, ISO), as applicable.

CSLB performs release on all primary packaging materials.

CCIT

CSLB performed CCIT for packaging material combinations associated with rVIII (same process approved for use in rIX-FP submission):

- 6 mL tubular glass injection vial ((b) (4)), closed with a (b) (4) stopper (b) (4) and sealed with a crimp cap (b) (4) .
- 10 mL tubular glass injection vial ((b) (4)), closed with a (b) (4) stopper (b) (4) and sealed with a crimp cap (b) (4) .

Container closure integrity testing of the packaging material combination was performed with samples from three media fill lots with the same packing material combinations to evaluate the integrity of the vial glass body, stopper, vial neck. A total number of (b) (4) samples from each lot were tested with the (b) (4) method using the (b) (4) test system according to testing instruction Q-52-A07.

(b) (4)

(b) (4)

Review Assessment/ Comments: Evidence of completed CCIT study is provided, with reference to relevant protocols. No objectionable findings noted.

14. Drug Product Stability

CSLB proposes shelf-life of 36 months for rVIII for the all fill sizes at 5°C and 3 months at 25°C

Completed stability studies (up to 36 months) or studies with ≥ 24 months data, include (b) (4) batches of rVIII-SingleChain DP tested under the temperature shift schemes and/or constant temperature studies all supporting the stability of the DP dosage forms.

The stability studies supporting the proposed shelf life, STR-808-011/-011A, STR-808-012, STR-808-013, STR-808-014, STR-808-016, STR-808-021 are ongoing and CSLB commits to continue the stability studies.

For future GMP follow-up studies of rVIII-SC, CSLB plans to introduce the (b) (4) test (b) (4).

Review Assessment/ Comments: For final DP container, sterility is tested at T₀ and 36 month test points. Endotoxin is tested at T₀ & 36 month test points. CSLB reports no sterility or endotoxin OOS to date.

CSLB has indicated that CCIT is performed Time 0; CSLB states in their submission that they plans to introduce the (b) (4) test (b) (4) at that time point, for future GMP follow-up studies of rVIII-SC. No objectionable findings noted. I defer the review of the Drug substance Stability to the Product Office Specialists.

(b) (4) Facility

The cGMP facility was inspected by DMPQ for PLI in (b) (4). The inspection was classified as VAI. In the last two years, (b) (4) was inspected by the (b) (4) Health and Medicines Authority (b) (4) for a Routine GMP inspection. No record of any prior US FDA inspection exists in OSAR.

Currently no other US approved, non-US approved, or investigational products are produced in the same rooms / areas used to produce rVIII-Single Chain Bulk Drug Intermediate (BDI). The product contact equipment used for the manufacture of rVIII-SingleChain is either dedicated or single use. No product contact equipment is shared with other US approved, non-US approved, or investigational products. The manufacturing area Line (b) (4) on the (b) (4) floor of (b) (4) is used for the manufacturing of rVIII-SingleChain BDI. According to CSLB, the manufacturing area Line (b) (4) equipment and utilities necessary for manufacturing rVIII-SingleChain at (b) (4) have been qualified.

Manufacture of rVIII-SingleChain is performed in campaigns and (b) (4)

(b) (4) possesses a quality agreement CSL Behring GmbH Marburg that defines responsibilities for BDI related processes such as manufacturing, testing/release, documentation/certification, transport/storage, change control, complaints/adverse events, and deviations.

According to (b) (4), the methods and procedures used in the manufacture of BDI are in conformance with cGMPs. In addition, all operations at the (b) (4) are conducted in compliance with applicable environmental laws and regulations.

(b) (4) manufacturing facility in (b) (4) consists of (b) (4) facility consists of (b) (4) floors with utility installations in (b) (4) and is a multi-product facility. Areas used in the manufacture and testing of BDI are:

(b) (4)

16. Medical transfer device

The only medical transfer device supplied with rVIII is a transfer device used for both transfer of sterile water for injection into the product vial and filtering of the reconstituted product before withdrawal into syringe. For ease of use, the Mix2 Vial device is provided together with an alcohol swab.

Review Assessment/ Comments: The Mix2Vial device is manufactured by Medimop; I confirmed that the device is a 510K cleared since 2003 (K031861). It is the same device used with rIX-FP, recently approved. No objectionable findings or further evaluation required.

17. Shipping Validation (Drug Product)

CSLB performed validation of shipping of drug product from Marburg, Germany (b) (4) [redacted], USA per Transport Validation Plan 5306842-01. The transport system (b) (4) is used in conjunction with a combination of transport by truck and airplane for finished products in the temperature range 2°C to 25 °C. (b) (4) [redacted]

(b) (4)

All acceptance criteria were met with no deviations reported.

Review Assessment/ Comments: DP Shipping appears complete; temperature graphs appear to coincide with data descriptions. No objectionable findings or further evaluation required.

18. Inspection Considerations

Note: Line items below are hyperlinked to the applicable section of this review memo, as applicable.

➤ None