CBER CMC BLA Review Memorandum

BLA STN 125661/0

Antihemophilic factor (recombinant), PEGylated-aucl

Zuben Sauna, PhD, Research Biologist
Ze Peng, PhD, Biologist
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1. BLA: STN 125661/0

2. APPPLICANT NAME AND LICENSE NUMBER

Bayer Healthcare LLC

3. PRODUCT NAME/PRODUCT TYPE

a. Non-Proprietary Name: antihemophilic factor (recombinant), PEGylated-aucl
b. Proprietary Name: JIVI
c. Company Code: BAY 94-9027
d. Common name: PEGylated recombinant B-domain-deleted coagulation factor VIII
e. CAS name: (b) (4)
f. International Non-Proprietary Name (INN): Damoctocog alfa pegol

4. GENERAL DESCRIPTION:

a. Pharmacological category: Antihemophilic Factor (Recombinant)
b. Dosage form: lyophilized powder for solution
c. Strength/Potency: single-use vials containing nominally (b) (4), 500, 1000, 2000, or 3000 International Units (IU)
d. Route of administration: intravenous use after reconstitution only
e. Indication: for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for:
   - On-demand treatment and control of bleeding episodes
   - Perioperative management of bleeding
   - Routine prophylaxis to reduce the frequency of bleeding episodes

5. CMC/QUALITY REVIEW TEAM:

Provide a list of CMC reviewers and identify the section(s) reviewed:

Reviewer/Affiliation	Section/Subject Matter
Zuben Sauna, Office of Tissues and Advanced Therapies (OTAT)/Division of Plasma Protein Therapeutics (DPPT)/ Hemostasis Branch (HB)	Drug Product
Ze Peng, OTAT/DPPT/HB	Drug Substance (exclude Characterization) and Adventitious Agents Safety Evaluation
Daniel Lagasse, OTAT/DPPT/HB	Section 3.2.S.3 Characterization and Section 3.2.S.4 Control of Drug Substance and Section 3.2.P.5 Control of Drug Product: analytical methods [(1)

	immunoassay for (b) (4) (2) immunoassay for (b) (4) (3) (b) (4) (4) (b) (4) (5) chromatography (b) (4) (6) (b) (4) (DP)] and relevant method validations

6. REVIEW SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

This review is an assessment of the CMC information in Biologics License Application (BLA), STN 125661/0, submitted by Bayer Healthcare LLC (Bayer), from a product quality perspective.

The product is Antihemophilic Factor (Recombinant), PEGylated-aucl; [INN: Damoctocog alfa], and its proprietary name for the US market will be JIVI. The active ingredient in JIVI is a recombinant analog of B-domain-deleted (BDD) coagulation factor VIII (FVIII) that contains an amino acid substitution at position 1804 (b) (4) cysteine (K1804C) within the FVIII A3 domain. The cysteine (b) (4) 60-kDa branched polyethylene glycol (PEG) moiety via maleimide conjugation. JIVI is indicated for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A for (i) On-demand treatment and control of bleeding episodes; (ii) Perioperative management of bleeding; and (iii) Routine prophylaxis to reduce the frequency of bleeding episodes.

The JIVI drug product (DP) is a lyophilized powder for reconstitution as a parenteral solution, supplied in single-use glass vials containing (b) (4) 500, 1000, 2000, and 3000 International Units (IU). It is reconstituted with 2.5 mL sterile Water for Injection (sWFI) prior to administration by intravenous injection.

We herein present a consolidated review of all the CMC/Product information provided by Bayer in the original BLA and subsequent amendments submitted in response to the Agency's information requests (IRs). These reviewers found the information provided in the original submission and in amendments as responses to our IRs to be sufficient to support the identity, quality, purity, safety, and potency of the product, JIVI.

B. RECOMMENDATION

The CMC (Product) reviewers recommend approval of BLA under STN 125661/0.

a. List of Drug Substance and Drug Product manufacturing facilities (refer to CTD section 3.2.A.1 of this Review Memo for a complete list of manufacturing and testing facilities).

b. There are no Post-Marketing Commitments (PMCs)/Post-Marketing Requirements (PMRs), from a CMC (Product) perspective for this BLA.

c. There are no lot release requirements for this product as it is manufactured using recombinant DNA technology.

7. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Zuben Sauna, PhD / Research Biologist / OTAT/DPPT/HB	Concur	
Ze Peng, PhD / Biologist / OTAT/DPPT/HB	Concur	
Daniel Lagasse, PhD / Staff Fellow / OTAT/DPPT/HB	Concur	
Tim Lee, PhD / Supervisory Research Chemist (Branch Chief) / OTAT/DPPT/HB	Concur	
Basil Golding, MD / Supervisory Medical Officer (Division Director) / OTAT/DPPT	Concur	

3.2.S DRUG SUBSTANCE

(b) (4)

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

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The DP is a lyophilized powder that is reconstituted with sterile water for injection. It is presented in the following dosages: (b) (4) 500, 1000, 2000 and 3000 IU/vial with a nominal fill size of 2.5 mL. The container is a glass vial, stoppered, and sealed with an aluminum seal and plastic flip top.

The composition of the DP is given below:

Ingredient	Quality	Function	Dose (IU/vial)				
			(b) (4)	500	1000	(b) (4)	3000
Damoctocog Alfa Pegol	(b) (4)	Active pharmaceutical ingredient	(b) (4)	500 IU	1000 IU	(b) (4)	3000 IU
Calcium Chloride (b) (4)	(b) (4)	Stabilizer	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Glycine	(b) (4)	Filler	(b) (4)	59 mg	59 mg	(b) (4)	59 mg
Histidine	(b) (4)	Buffering agent	(b) (4)	8.4 mg	8.4 mg	(b) (4)	8.4 mg
Sodium Chloride	(b) (4)	Stabilizer	(b) (4)	4.7 mg	4.7 mg	(b) (4)	4.7 mg
Sucrose	(b) (4)	Stabilizer	(b) (4)	27 mg	27 mg	(b) (4)	27 mg
Polysorbate 80	(b) (4)	Surfactant, Stabilizer	(b) (4)	216 µg	216 µg	(b) (4)	216 µg
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

JIVI is a PEGylated, B-domain-deleted recombinant Factor VIII product, designed for a longer circulation half-life. The DP has the same formulation excipient composition as Bayer's commercial rFVIII products. A single fill size (2.5 mL) was developed for all (b) (4) JIVI DP dosages. The JIVI formulation and process development strategy was based on the successful demonstration of stability from development studies, pre-clinical and clinical lots, and process experience with Bayer's commercial rFVIII formulation. Data from the development studies and clinical manufacturing experience demonstrated satisfactory stability results. No changes were made to the DP formulation between development, clinical studies, and conformance lots.

3.2.P.2.1.2 Excipients

The DP contained the same concentrations of excipients for all presentations. These are listed below:

Name of Excipient	Concentration	Function
Calcium Chloride (b) (4)		Stabilizer

Glycine	(b) (4)	Filler for lyophilized product
(b) (4)-Histidine	(b) (4)	Stabilizer
Polysorbate 80	(b) (4)	Stabilizer
Sodium Chloride	(b) (4)	Stabilizer
Sucrose	(b) (4)	Stabilizer
(b) (4)	(b) (4)	(b) (4)

3.2.P.2.2 Drug Product (in the context of Pharmaceutical Development)

3.2.P.2.2.1 Formulation Development

The DP formulation evaluated in development studies contains the same excipient composition as the formulations currently used for Bayer's commercially approved rFVIII products. (b) (4) demonstrate satisfactory DP stability. The (b) (4) dosages were prepared and freeze-dried using the commercial rFVIII lyophilization cycles for 2.5 mL fill size. The lyophilized samples were stored at various temperatures to assess stability.

Potency, measured in the chromogenic assay, was the primary stability-indicating parameters for JIVI. The JIVI formulation was assessed to meet a minimum shelf-life target of (b) (4) of the initial potency under the intended storage conditions (24 months at 5°C).

Overall, the stability as estimated based on potency results, demonstrated that the selected formulation provides desirable stability for JIVI DP with dosage strengths ranging from (b) (4). The following assays/tests were carried out as part of the stability assessment:

Assay/Test	Acceptance criterion
Visual appearance before reconstitution	White to slightly yellow
Visual appearance after reconstitution	Clear liquid
Solubility time	(b) (4)
rFVIII Potency by chromogenic assay	(b) (4)
pH	6.6 to (b) (4)
Clarity (b) (4))	(b) (4)
Moisture (%)	(b) (4)
(b) (4)	
Purity (b) (4)	

During the development of JIVI, there were no differences between clinical and commercial formulations of the final DP.

Reviewer's Assessment: The JIVI DP formulation was shown to demonstrate satisfactory stability results in developmental, pre-clinical and clinical studies. The same formulation will be used for commercial manufacture.

3.2.P.2.3 Manufacturing Process Development (in the context of Pharmaceutical Development)

The strategy for DP process development was to apply Bayer's current commercial rFVIII manufacturing processes to the manufacture of JIVI and assess the quality of the product. The steps involved in the bulking and filling phase of manufacture of DP are:

- (b) (4)
- Sterile filtration (b) (4)
- Final formulation
- Filling into vials

Differences between the current commercial rFVIII manufacturing process and that used for JIVI are summarized below:

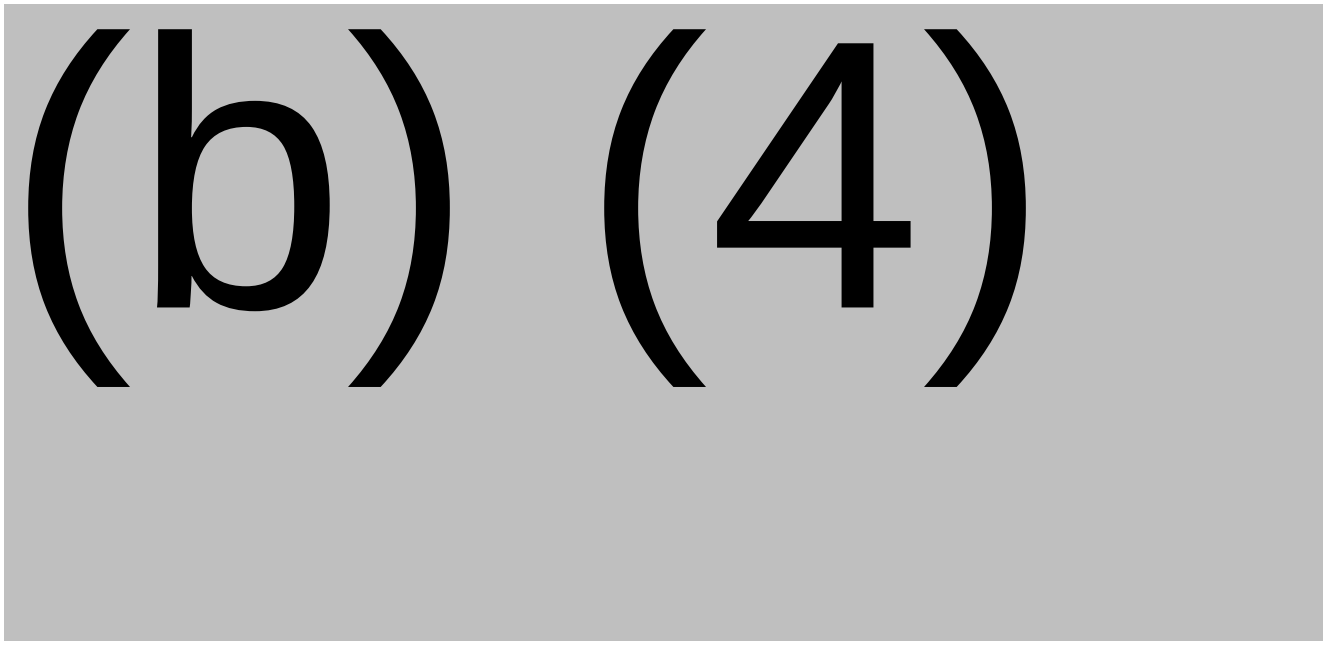
1. The JIVI (b) (4)
2. For JIVI, all dosage strengths ((b) (4) - 3000 IU/vial) are produced with 2.5 mL fill size, whereas for rFVIII processes there are (b) (4)
3. During the manufacture of JIVI, Polysorbate 80 is added (b) (4) manufacture, rather than during the (b) (4)

No changes were made in the manufacturing process, facilities and equipment between Phase III clinical batches and conformance batches.

Studies carried out using (b) (4) process development studies were carried out to demonstrate that the commercial rFVIII bulking and filling processes, combined with the commercial rFVIII freeze-drying process for 2.5 mL fill size, were suitable for the manufacture of JIVI. (b) (4) studies, including (b) (4) filling, and subsequent freeze-drying, were conducted using (b) (4) equipment to simulate the production scale commercial rFVIII processes for 2.5 mL fill size.

A (b) (4) approach was used in these studies covering the (b) (4) dosages. The test results for these (b) (4) development batches are provided below:

(b) (4)



Reviewer's Assessment: The bulking and sterile filling processes used for JIVI were evaluated for release acceptance criteria in (b) (4) *developmental batches.* (b) (4) *batches* (b) (4) *met acceptance criteria for all release tests. The bulking and sterile filling processes are suitable for the manufacture of JIVI DP.*

3.2.P.2.4 Container Closure System (in the context of Pharmaceutical Development)
The container and closure system intended for commercial application for the JIVI is composed of a glass vial and stopper, sealed with an aluminum seal. JIVI DP is a lyophilized powder for injection and has the same dosages, excipient composition, and fill volume (2.5 mL) as Bayer's commercial rFVIII products. The usability, safety and effectiveness of the commercial rFVIII primary packaging system has been successfully demonstrated with Bayer's rFVIII products and with JIVI during clinical studies. The reconstitution cap and aluminum seal, which were already licensed for the commercial rFVIII have been used for the JIVI DP used in clinical studies. There will be no changes for the commercial JIVI product.
The compatibility studies of primary packaging components were performed with reconstituted JIVI DP. Potency, (b) (4), total protein, clarity and particulate matter were evaluated, and compatibility was demonstrated.
Extractable studies were also performed on the DP primary packaging components and demonstrated to be acceptable for use.

Reviewer's Assessment: The section 3.2.P.2 is satisfactory as submitted. The JIVI manufacturing process is the same as that used for the licensed rFVIII DP with minimal modifications. The effects of these changes and the PEGylation step have been adequately characterized.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Manufacturing sites associated with the JIVI DP are provided below:

Address	Manufacturing steps associated with the site(s)

Bayer HealthCare LLC (b) (4)	Manufacture of bulk product Primary packaging Secondary packaging QA Product Release
Bayer HealthCare LLC (b) (4)	Quality Control Testing, Stability Storage and Testing
Bayer HealthCare LLC (b) (4)	

3.2.P.3.2 Batch Formula

Definition of batch: (b) (4) DP that is prepared from (b) (4) , and sterile filtered. Each batch is assigned a unique batch number.

Batch sizes are summarized below:

Nominal Dosage (IU/vial)	Minimum No. of Vials	Maximum No. of Vials
(b) (4)	(b) (4)	
500	(b) (4)	(b) (4)
1000	(b) (4)	(b) (4)
2000	(b) (4)	(b) (4)
3000	(b) (4)	(b) (4)

The quantities of excipients for the minimal batch size of (b) (4) vials (for all doses) are:

Component	Weight (kg)
Calcium Chloride (b) (4)	(b) (4)
Glycine	(b) (4)
Histidine	(b) (4)
Sodium Chloride	(b) (4)
Sucrose	(b) (4)
Polysorbate 80	(b) (4)
(b) (4)	(b) (4)

Reviewer's Assessment: The sections 3.2.P.3.1 and 3.2.P.3.2 are adequately described and no deficiencies were identified. At the DP stage, the JIVI manufacturing process is the same as that used for the licensed rFVIII DP and occurs at the same location. This manufacturing process thus has a proven track record of generating a safe product.

3.2.P.3.3 Description of Manufacturing Process

The steps in the manufacturing process for JIVI DP and the process parameters are summarized below:

Process step	Purpose	Process parameters	Process performance attributes
		(b) (4)	

	(b) (4)
(b) (4)	
Sterile filtration	
(b) (4)	
Filling	
Stopper placement on filled vials	
Freeze Drying	

	(b) (4)		
Sealing	Each vial is crimped with an aluminum seal with plastic flip-off top under aseptic conditions		

Reviewer's Assessment: The section 3.2.P.3.3 is satisfactory as submitted. The process steps, and process performance attributes are based on decades of experience that this manufacturer has with the licensed rFVIII DP.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The following steps were deemed critical during the manufacture of the DP:

(b) (4)

The maximum processing times for the manufacturing steps are:

(b) (4)

(b) (4)

Reviewer's Assessment: The section 3.2.P.3.4 is acceptable as submitted. The critical control parameters for the JIVI DP manufacturing process are adequate. The action limits based on historical data and experience can assure product quality. The process hold times (b) (4) *filling processes) were confirmed during process validation.*

3.2.P.3.5 Process Validation and/or Evaluation

Validation approach: The DP conformance batches were manufactured from QA released conformance (b) (4)

For evaluating the DP process, Bayer used a (b) (4) of JIVI at the (b) (4) DP vials from the conformance batches were included in a stability program. The dosage strengths and maximum and minimum (b) (4) conformance lots are summarized below:

Dosage Strength (IU/vial)	Protocol Requirement	Minimum Load Run(s) Completed	Maximum Load Run(s) Completed	Number of Conformance Lots
(b) (4)	(b) (4)			
500				
1000				
2000				
3000				

The DP conformance batches described above were manufactured to demonstrate the consistency and reproducibility of the manufacturing process at commercial scale when operated within predetermined operational parameter ranges and set points. Additional details of the process validation are provided below:

Process hold times: The maximum process hold times for (b) (4) ll quality attributes met all acceptance criteria.

(b) (4) (b) (4)

(b) (4)

Validation of Sterile Filtration: The manufacturing process includes a sterile filtration step during which the (b) (4)

All acceptance criteria were met.

Validation of Aseptic Filling: (b) (4)

Reviewer's Assessment: The section 3.2.P.3.5 is satisfactory as submitted. The overall validation approach which relies on a (b) (4) *approach is acceptable. The data presented in this section cover validation of all steps in the manufacture of JIVI DP, i.e.* (b) (4) *, sterile filtration, aseptic filling and freeze drying. The effects of these changes and the PEGylation step have been adequately characterized. Moreover, Bayer has challenged the manufacturing process to show that the maximum process hold times for* (b) (4) *filling processing do not adversely affect product quality.*

3.2.P.4 Control of Excipients

The control of excipients used in the manufacture is summarized below:

	(b) (4) .
Calcium chloride (b) (4)	(b) (4)
Glycine	
(b) (4) -Histidine	
Polysorbate 80	

	(b) (4)
Sodium chloride	
Sucrose	

There were no non-compendial specifications for excipients that required in-house tests.

3.2.P.4.5 Excipients of Human or Animal Origin

This product does not contain excipients of human or animal origin.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The specifications for JIVI DP and the justification for these are provided below:

Analytical method	Specification					Justification
	(b) (4)	500 IU/vial	1000 IU/vial	2000 IU/vial	3000 IU/vial	
Visual before reconstitution	White to slightly yellow					These release specifications were based on the historical range for clinical Phase III data and the release specifications for rFVIII-FS
Visual after reconstitution	Clear liquid					
Clarity	(b) (4)					
Color determination	(b) (4)					
Solubility time	(b) (4)					
pH	6.6 to 7.0					
(b) (4)	(b) (4)					
Moisture (%)	(b) (4)					
Particulate Matter Number of Particles/vial (b) (4)	(b) (4)					
Particulate Matter Number of Particles/vial (b) (4)	(b) (4)					
Purity	(b) (4)					Statistical analyses* of manufacturing data from (b) (4) Phase III clinical batches and (b) conformance batches (b) (4) were used to justify specifications. (b) (4) .
(b) (4)	(b) (4)					
(b) (4)	(b) (4)					
(b) (4)	(b) (4)					
Potency (IU/vial), minimum	(b) (4)					
Potency (IU/mL) minimum	(b) (4)					
Specific Activity	(b) (4)					
Total protein (µg/vial)	(b) (4)					
Total protein (µg/mL)					(b) (4)	
Sterility	No microbial growth observed (b) (4)					Based on the historical range for release specifications for rFVIII-FS
Endotoxin (b) (4)	(b) (4)					
Glycine	(b) (4)					(b) (4)
Histidine	(b) (4)					
Sucrose	(b) (4)					
Sodium	(b) (4)					
Calcium	(b) (4)					
Polysorbate 80	(b) (4)					

(b) (4)

Note on potency assignment: Potency of JIVI is measured using a chromogenic assay. The chromogenic (b) (4) . The assay was adequately validated by Bayer (see also review memo from OCBQ/DBSQC). (b) (4) .

Reviewer's Assessment: The sections 3.2.P.5.1 & 3.2.P.5.6 are satisfactory as submitted. The specifications have been justified based on one of three approaches: (i) Historical data of batches manufactured for clinical studies. (ii) Statistical analyses (described above). (iii) They are based on (b) (4) *. These methods have been appropriately applied to the individual analytical methods described in sections 3.2.P.5.2 and 3.2.P.5.3.*

Here we have reviewed the test for the (b) (4) . All other tests and analytical procedures have been reviewed by DBSQC:

(b) (4)

These specifications apply to DP release and shelf-life for (b) (4) 500, 1000, 2000, and 3000 IU.

Particulate Matter Justification of Specification:

The particulate matter release specification limits (b) (4) requirements are set for DP release and shelf-life.

Reviewer's Assessment: Sections 3.2.P.5.1 and 3.2.P.5.6 are acceptable as submitted and no deficiencies were identified. Particulate matter release specification limits were set as per (b) (4) *requirements and are acceptable as submitted.*

3.2.P.5.4 Batch Analyses

The lots used in batch analyses and their disposition is summarized below:

Presentation (b) (4) IU:

Batch Number:	(b) (4)
Date of Manufacture:	
Drug Substance Batch:	
Batch Size:	
Use of the Batch:	

Presentation 500 IU:

Batch Number:	(b) (4)
Date of Manufacture:	
Drug Substance Batch:	
Batch Size:	
Use of the Batch:	

Presentation 1000 IU

Batch Number:	
Date of Manufacture:	
Drug Substance Batch:	
Batch Size:	
Use of the Batch:	

Presentation 2000 IU:

Batch Number:	(b) (4)
Date of Manufacture:	
Drug Substance Batch:	
Batch Size:	
Use of the Batch:	

Presentation 3000 IU

Batch Number:	
Date of Manufacture:	
Drug Substance Batch:	
Batch Size:	
Use of the Batch:	

All batches listed above were tested for the following parameters:

- Appearance After Reconstitution
- Appearance Before Reconstitution

- Calcium
- Clarity
- Color
- Potency (b) (4))
- Potency ((b) (4)
- Glycine
- Histidine
- (b) (4)) Identity
- (b) (4)
- (b) (4) % Purity
- (b) (4) Identity
- (b) (4)
- (b) (4) Purity
- Endotoxin (b) (4)
- Moisture-(b) (4)
- pH
- (b) (4)
- Polysorbate 80
- (b) (4)
- (b) (4) Total Protein
- (b) (4) Total Protein per Vial
- Sodium
- Solubility Time
- (b) (4) Specific Activity
- Sterility
- Sucrose
- Maximum Number of Particles (b) (4)
- Maximum Number of Particles (b) (4)
- (b) (4)

All batches met the acceptance criterion.

(b) (4)

For the commercial conformance campaign, (b) (4) DP lots were manufactured at the proposed commercial manufacturing site (Bayer (b) (4) (b) (4) Batch genealogy is available for all lots, providing traceability from raw materials to final container. The DP batch numbers and dates of manufacture of the commercial conformance lots are summarized as follows:

(b) (4)

All commercial conformance DP lots met release criteria and support consistency of product manufacture.

Reviewer's Assessment: The sections 3.2.P.5.4 & 3.2.P.5.5 are satisfactory as submitted. The lots used in batch analyses show an acceptable distribution of the different JIVI DP presentations. The tests used for batch analyses are comprehensive and sufficient to ensure product quality. According to batch analysis data, the amount of particulate matter (b) (4) *or greater) quantified in the commercial conformance lots* (b) (4) *) is significantly lower than detected in Phase III Clinical lots* (b) (4) *This trend suggests that Bayer has improved manufacturing processes resulting in fewer particles, suggesting a greater product quality and patient safety.*

(b) (4)

(b) (4)

Future reference standards for commercial production: An established protocol will be followed to introduce product reference standards in the future. Relevant testing, as described above, would be carried out and assurance of comparability would be established.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

All clinical drug-product batches discussed in the stability study were manufactured in the same facility using Bayer's commercial rFVIII drug-product process and the container closure system intended for commercial application. These batches may, therefore, be considered representative of commercial DP stability. The stability strategy included a (b) (4) approach for the conformance batches based on the (b) (4) respectively). These dosage strengths (b) (4) all JIVI dosage strengths. In addition, since the clinical and proposed commercial manufacturing processes for JIVI are identical, the use of both clinical and conformance batches to demonstrate stability of the individual dosage strengths is justified. When combining the clinical and conformance batches, at least (b) (4) of each dosage strength was produced. Summary of batches on stability study:

Dosage Strength	Clinical Batches	Conformance Batches
(b) (4)	(b) (4)	
500 IU		
1000 IU		
2000 IU		
3000 IU		

The intended shelf life for JIVI DP at 2-8°C is 24 months from the date of manufacture. Within this period, the DP may be stored for up to 6 months at a temperature up to 25°C, or up to 3 months at a temperature up to (b) (4). For the stability studies the samples were stored under a wide variety of conditions:

Samples are stored for (b) (4) months at 5°C.

Samples are stored for 18 months at 5°C followed by storage at (b) (4)

Samples are stored for 21 months at 5°C followed by storage at (b) (4)

Samples are stored for 24 months at 5°C (b) (4) (b) (4)

Samples are stored for (b) (4) months at 5°C followed by storage at (b) (4)

(b) (4)

vials are placed on stability program at 5°C for 18 months, (b) (4)

vials are placed on stability program at 5°C for 21 months, (b) (4)

vials are placed on stability program at 5°C for 24 months, (b) (4)

vials are placed on stability program at 5°C for (b) (4) months, (b) (4)

Samples are stored for 18 months at 5°C, then moved to 25°C (b) (4)

Samples are stored for 21 months at 5°C, (b) (4)

stored for 18 months at 5°C followed by (b) (4)

Samples are stored for 24 months at 5°C, (b) (4)

Samples are stored for (b) (4) months at 5°C, (b) (4)

The results of these stability studies (even under (b) (4) conditions) support the proposed shelf-life of the product (24 months at 2-8°C and storage for up to 6 months at a temperature up to 25°C within this time-period).

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Bayer has provided the following post-approval commitment for an ongoing stability program. For each calendar year in which manufacturing is performed, (b) (4) JIVI drug-product (b) (4) of each fill size will be placed on stability. The descriptions of the cycle conditions are: (i) storage for 18 months at 5°C followed by storage at 25°C (b) (4) for the remainder of the study for a total of (b) (4) months, and (ii) storage 21 months at 5°C followed by storage at (b) (4) for the remainder of the study for a total of (b) (4) months.

Reviewer's Assessment: The section 3.2.P.8 is satisfactory as submitted. The batches used in the stability studies for JIVI drug-product involve a diversity of storage conditions (see above for details). Together these storage conditions demonstrate that the product quality is maintained (i) under the recommended storage conditions and (ii) even when stressed by different storage conditions likely to occur in real-world conditions. Bayer used a (b) (4) approach, i.e. (b) (4) dosage strengths of conformance lots were used in the stability studies. However, since the clinical and proposed commercial manufacturing processes for JIVI are identical, the use of both clinical and conformance batches to demonstrate stability of the individual dosage strengths may be justified. When combining the clinical and conformance batches, at least (b) (4) of each dosage strength was produced. Thus, overall, robust evidence has been provided to support the proposed shelf-life of the JIVI drug-product. JIVI is intended for use immediately after reconstitution. The post-reconstitution potency of conformance and clinical lots was evaluated after (b) (hours at room temperature and was found to meet the stability acceptance criteria.

3.2.A.2 Adventitious Agents Safety Evaluation

1) Control of non-viral adventitious agents

For the non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled through the use of: (1) appropriate environmental control monitoring in the manufacturing process; (2) in-process controls, e.g., testing for microbial growth (b) (4) . The potential of JIVI to be contaminated with non-viral adventitious agents is further reduced by testing the final product for Sterility, and Endotoxin. Bayer manufactures JIVI according to GMP regulations.

No human or animal derived raw materials are used in the manufacture of JIVI. No raw materials or ingredients of human or animal origin are used in the formulation of JIVI DP. Additionally, routine cleaning procedures in the manufacturing process of JIVI include sanitization of equipment with (b) (4) , for the removal and/or inactivation of potential contaminations of viruses. Thus, the potential risk of contaminating adventitious viruses or transmissible spongiform encephalopathy agents is minimized.

2) Testing the capacity of the JIVI purification process to clear viruses

(b) (4)

(b) (4) . These viruses resemble viruses which may contaminate the JIVI product, and represent a wide range of physico-chemical properties that test the ability of the manufacturing process to eliminate viruses. Virus clearance studies were performed by (b) (4) Virus inactivation and/or removal by the respective step(s) were tested at (b) (4)

Reviewer's Assessment: To evaluate the adequacy of the viral clearance data in each study, each (b) (4) *system used needs to be qualified whereas these data were incomplete in the original BLA submission. Therefore, I requested Bayer to provide the qualification data to demonstrate that each* (b) (4) *system used for viral clearance studies is representative of the respective manufacturing step at the proposed commercial scale, which include* (b) (4) *This request was sent to Bayer on 5 March 2018, and they responded in an amendment on 16 March 2018. The information provided in this amendment and the viral clearance data from the original BLA submission are summarized below:*

- (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

Reviewer's Assessment: Virus selection in the (b) (4) *studies is consistent with the FDA recommendation regarding the biological drug products derived from cell lines of human or animal origin. The qualification of the* (b) (4) *used for viral clearance is acceptable, and the viral clearance data derived from these* (b) (4) *are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process. The mechanism for viral clearance between the* (b) (4) *. To avoid overestimating its viral clearance capacity, I used the data generated from* (b) (4) *Thus, Bayer provided sufficient and adequate data to demonstrate effectiveness of the developed purification process to clear a wide range of viruses and ensure product safety.*