DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
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To: Administrative File: STN 125661/0

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Applicant: Bayer Healthcare LLC, US License # 0008

Product: Antihemophilic Factor (Recombinant), PEGylated (Product Code: BAY 94-9027); Trade Name: Jivi

Indication: Treatment of Hemophilia A (congenital Factor VIII deficiency)

Subject: Final Review Memo (BLA): Seeking licensure for new product, Antihemophilic Factor (Recombinant), PEGylated to be used in the treatment of Hemophilia A

Due Date: PDUFA Action Due Date: August 30, 2018 (Note, OTAT Office Director target action due date: August 16, 2018)

SUMMARY

Bayer Healthcare LLC (hereafter referred to as Bayer) has submitted an original Biologics License Application (BLA) seeking approval for a new product, Antihemophilic Factor (Recombinant), PEGylated (trade name granted: Jivi), to be used in the treatment of Hemophilia A. Bayer is currently approved for the manufacture and distribution of other similar antihemophilic factor products, Kogenate/Kogenate-FS, which has been approved since 1993 (BL 103332), and for Kovaltry which was approved on March 16, 2016 (STN 125574/0).

The drug substance and drug product manufacture of the antihemophilic factor products (Kogenate/ Kogenate-FS, Kovaltry, Jivi) all occur at Bayer's campus in (b) (4) As with the other antihemophilic products, Jivi is supplied as a lyophilized powder and requires reconstitution with sterile water for injection diluent before administration. The diluent will be supplied in a pre-filled syringe

format and is manufactured by two different suppliers, (b) (4) Bayer (b) (4) The delivery of Jivi requires medical device products as provided in the administration kit with the drug product and diluent (noted as the market packages). The kits are the same or are similar to the kits provided with Kovaltry; therefore, a CDRH consult was determined by OTAT to not be necessary as a consult for this BLA.

The submission was appropriately filed as a BLA according to 21 CFR 601.12a. The BLA was submitted via the eCTD format and was received by CBER on August 30, 2017. The following sections were provided in the BLA; the responsible office (DMPQ or OTAT) is denoted for each section:

Module 1: Regional [DMPQ/OTAT]

1.1 FDA Forms 365h, 3674, and 3397
1.2 Cover Letter
- Cover Letter [All]
- Reviewer's Guide [All]

1.3 Administrative Information [OTAT]
- Debarment Certification
- Financial Certification and Disclosure (FDA Form 3454 and FDA Form 3455)

1.4 References
- Letters of Authorization (6) for Drug Master Files for container closure items and device components and 510(K) [OTAT/DMPQ]
- Cross-Reference to Previously Submitted Information (for Kogenate-FS and Kovaltry)

1.6 Regulatory Meetings and Response Summaries [DMPQ/OTAT]
1.12 Other Correspondence
- Application for Product Name, Trademark naming rights [OTAT]
- Environmental Analysis – Categorical Exclusion [DMPQ]

1.13 Annual Report (Investigation Plan) [OTAT]
1.14 Labeling [OTAT]
1.16 Risk Management Plan (Pharmacovigilance) [OTAT]
1.18 Proprietary names [OTAT]

Module 2: Common Technical Document Summaries [DMPQ/OTAT]

2.2 Introduction
2.3 Quality Overall Summary
- Introduction
- Drug Substance: (b) (4) (Bayer) [OTAT/DMPQ]
- Drug Substance: (b) (4) OTAT]
- Drug Product – Lyophilized Product (Bayer) [OTAT/DMPQ]
- Drug Product – Sterile Diluent (b) (4) [OTAT/DMPQ]
- Drug Product – Sterile Diluent (Bayer (b) (4)) [OTAT/DMPQ]
- Drug Product – Facility and Equipment Info [DMPQ], Adventitious Agents [OTAT]
- Diluent (b) (4) – Facility and Equipment Info [DMPQ], Adventitious Agents [OTAT]
- Diluent (Bayer (b) (4) – Facility and Equipment Info [DMPQ], Adventitious Agents [OTAT]
- Medical Devices [OTAT]

2.4 Nonclinical Overview [OTAT]

- Pharmacology, Pharmacokinetics, Toxicology

2.5 Clinical Overview [OTAT]
2.6 Nonclinical Written and Tabulated Summaries [OTAT]
2.7 Clinical Summary [OTAT]

Module 3: Quality

3.2.S Drug Substance: (b) (4) (Bayer)

3.2.S.1 General Information [OTAT]
- Nomenclature, Structure, General Properties

3.2.S.2 Manufacture
- Manufacturing Sites [DMPQ]
- Manufacturing Process Flow Diagrams [OTAT/DMPQ]
- Raw Material Specifications & Testing [OTAT]
- Validation of Intermediate Test Methods, Control of Intermediates [OBRR]; (b) (4) [DMPQ]
- Process Validation [OTAT/DMPQ]
  - Process Validation Summary
  - Process validation – (b) (4) /Cell Culture
  - Process Validation – Harvest and Isolation
  - Process Validation – Purification
  - Process Evaluation
- Manufacturing Process Development [OTAT]

3.2.S.3 Characterization [OTAT]
3.2.S.4 Control of Drug Substance
- Specification [OTAT]
- Analytical Test Procedures [OTAT] (b) (4) – DMPQ)
- Validation of Analytical Procedures [OTAT] (b) (4) – DMPQ)
- Batch Analyses [OTAT/DMPQ]
- Justification of Specification [OTAT]

3.2.S.5 Reference Standards or Materials [OTAT]
3.2.S.6 Container Closure System [DMPQ/OTAT]
3.2.S.7 Stability [OTAT]

3.2.P Drug Product (Lyophilized Product – Bayer)

3.2.P.1 Description and Composition of the Drug Product [DMPQ/OTAT]
3.2.P.2 Pharmaceutical Development [OTAT/DMPQ]
- Drug Product and Excipients
- Manufacturing Process
- Container Closure – System, Integrity Testing, Compatibility, Functionality
- Extraction Studies

3.2.P.3 Manufacture
- Manufacturing Site (b) (4)) [DMPQ]
- Batch Formula [OTAT]
- Description of Manufacturing Process and Process Control [OTAT/DMPQ]
  - Bulk/Filling

        - Freeze Drying
        - Inspection and Warehouse
        - Batch Numbering System
    - Control of Intermediates and Critical Steps (Bulk/Filling, Freeze Drying, Inspection/Warehouse) [OTAT]
    - Process Validation [OTAT/DMPQ]
        - Process Validation Summary
        - Process Validation – Bulk/Filling
        - Process Validation – Freeze Drying

3.2.P.4 Control of Excipient [OTAT]

3.2.P.5 Control of Drug Product

- Release and Shelf Life Specifications [OTAT]
- Analytical Test Procedures [DBSQC]
- Validation of Analytical Procedures [DBSQC]
- Batch Analyses [OTAT/DMPQ]
- Characterization of Impurities [OTAT]
- Justification of Specification [OTAT]

3.2.P.6 Reference Standards or Materials [OTAT]

3.2.P.7 Container Closure System

- Description of Packaging Materials – Reconstitution cap, seal, vial, stopper [DMPQ]
- Specification and Test procedure – vial, cap, stopper [DMPQ]
- Drawings of Packaging Materials [DMPQ]

3.2.P.8 Stability [OTAT]

3.2.P Drug Product (Sterile Diluent – (b) (4)

3.2.P.1 Description and Composition of the Sterile Diluent – Pre-filled Syringe (2.5 mL) [DMPQ/OTAT]

3.2.P.2 Pharmaceutical Development [OTAT/DMPQ]

- Drug Product
- Container Closure – System, Integrity Testing

3.2.P.3 Manufacture

- Manufacturing Site ((b) (4)) [DMPQ]
- Batch Formula [OTAT]
- Description of Manufacturing Process and Process Control [OTAT/DMPQ]
- Control of Intermediates and Critical Steps [OTAT]
- Process Validation [OTAT/DMPQ]
    - Process Validation – 2.5 mL Prefilled syringe

3.2.P.5 Control of Drug Product [OTAT]

- Release and Shelf Life Specifications
- Batch Analyses

3.2.P.7 Container Closure System [DMPQ]

- Description of Packaging Materials – Reconstitution cap, seal, vial, stopper
- Specification and Test procedure – vial, cap, stopper
- Drawings of Packaging Materials

3.2.P.8 Stability [OTAT]

3.2.P Drug Product (Sterile Diluent – Bayer (b) (4)
- 3.2.P.1 Description and Composition of the Sterile Diluent – Pre-filled Syringe (2.5 mL) [DMPQ/OTAT]
- 3.2.P.2 Pharmaceutical Development [OTAT/DMPQ]
  - Drug Product
  - Container Closure – System, Integrity Testing
- 3.2.P.3 Manufacture
  - Manufacturing Site (b) (4)) [DMPQ]
  - Batch Formula [OTAT]
  - Description of Manufacturing Process and Process Control [OTAT/DMPQ]
  - Control of Intermediates and Critical Steps [OTAT]
  - Process Validation [OTAT/DMPQ]
    - Process Validation – 2.5 mL Prefilled syringe
    - Process Validation – 2.5 mL Sterilization
- 3.2.P.5 Control of Drug Product [OTAT]
  - Release and Shelf Life Specifications
  - Batch Analyses
- 3.2.P.7 Container Closure System [DMPQ]
  - Description of Packaging Materials – Reconstitution cap, seal, vial, stopper
  - Specification and Test procedure – vial, cap, stopper
  - Drawings of Packaging Materials
- 3.2.P.8 Stability [OTAT]

3.2.A Appendices
- 3.2.A.1 Facilities and Equipment (Bayer – (b) (4)) [DMPQ]
  - Facilities and Equipment Summaries for DS and DP ((b) (4)
  - Qualification/Validation of Facilities and Equipment
  - Facility Floor Diagrams
  - Personnel Flow Diagrams
  - Raw Material and Waste Flow Diagrams
  - Intermediate Product Flow Diagrams
  - Finished Goods Flow Diagrams
  - Room Utilization Flow Diagrams
  - Cross-Contamination control summary
  - Site Overview – Use of Buildings
  - Environmental Monitoring Program
  - Batch Record Documentation
  - Multi-Product Descriptions for Buildings (b) (4)
- 3.2.A.1 Facilities and Equipment (b) (4) [DMPQ]
  - Site Overview – Use of Buildings for manufacture of 2.5 mL pre-filled syringe
- 3.2.A.1 Facilities and Equipment (Bayer (b) (4)) [DMPQ]
  - Site overview

- Qualification/validation of bulk/filling equipment
- Environmental Monitoring Program

3.2.A.2 Adventitious Agents Safety Evaluation (Lyophilized Drug Product – Bayer) [OTAT]

- TSE Assessment – Raw materials, drug product
- Virological Safety – Cell Bank
- Clearance Testing
- Study Reports of Virus Clearance Validation

3.2.A.2 Adventitious Agents Safety Evaluation (Sterile Diluent - (b) (4)) [OTAT]

- TSE Assessment – Sterile Diluent pre-filled syringe

3.2.A.2 Adventitious Agents Safety Evaluation (Sterile Diluent – Bayer (b) (4)) [OTAT]

- TSE Assessment – Sterile Diluent pre-filled syringe

3.2.R Regional Information

- Executed Batch Records [OTAT]
- Method Validation Reports [OTAT/DBSQC] (b) (4) DS – DMPQ)
- Shipping Study [DMPQ]
- Device Description – Vial Adapter [OTAT]
- Product Specification and Test Procedure – Vial Adapter [OTAT]
- Human Factor Study Report – Device [OTAT] (*previously reviewed by CDRH for Kovaltry)
- Risk Management Report [OTAT/DMPQ]
- Device Description – Administration Set [OTAT] (*previously reviewed by CDRH for Kovaltry)
- Product Specification and Test Procedure – Administration Set [OTAT] (*previously reviewed by CDRH for Kovaltry)
- Device Description – Winged Infusion Set [OTAT] (*previously reviewed by CDRH for Kovaltry)
- Drawing – Winged Infusion Set [OTAT]

3.3 Literature References [OTAT]

<u>Module 4: Nonclinical Study Reports</u> [OTAT]

4.2.1 Pharmacology
4.2.2 Pharmacokinetics
4.2.3 Toxicology
4.3 Literature References

<u>Module 5: Clinical Study Reports</u> [OTAT]

5.2 Listing of Clinical Sites
5.3.1 Reports of Biopharmaceutics Studies
5.3.3 Reports of Human Pharmacokinetic Studies
5.3.5 Reports of Efficacy and Safety Studies
5.4 Literature References

Amendments

During the review cycle, DMPQ requested additional information in order to complete an adequate review. The following is a summary of the Amendments which contained the responses to the DMPQ information requests:

- Amendment #26: DMPQ IR #1 for clarification on drug substance process validation, media fills, drug product equipment qualification and cleaning, and the categorical exclusion for an environmental assessment. (IR sent March 1, 2018, CBER receipt date of Amendment March 23, 2018, Sequence No. 0026)
- Amendment #31: DMPQ IR #2 requesting information on the drug substance manufacturing equipment. (IR sent April 6, 2018, CBER receipt date of Amendment: April 13, 2018; Sequence No. 0032)
- Amendment #36: DMPQ IR #3 requesting information on drug substance process validation, drug product shipping validation, and labeling and packaging activities. (IR sent April 20, 2018, CBER receipt date of Amendment: May 4, 2018; sequence no. 0037).
- Amendment #42: DMPQ IR #4 regarding a second distribution site for finished market packages of Jivi. (IR sent May 21, 2018, CBER receipt date of Amendment: May 25, 2018; Sequence No. 43).
- Amendment #48: DMPQ IR #5 regarding membrane cleaning data, purification cleaning data, filling equipment cleaning, and finished package transport information. (IR sent June 6, 2018, CBER receipt date of Amendment: June 20, 2018; Sequence No. 49).
- Amendment #49: DMPQ IR #6 for revised categorical exclusion to contain language specific to 21 CFR Part 25.15(d). (IR sent June 27, 2018, CBER receipt date of Amendment: June 28, 2018; Sequence No. 50).

Reviewer Recommendation: Approval of the BLA is recommended from a DMPQ viewpoint. No post-marketing commitments or inspectional recommendations have been identified.

REVIEW MEMO TABLE OF CONTENTS

BACKGROUND

With this BLA, Bayer is seeking approval of a new antihemophilic Factor (recombinant) PEGylated product, Jivi (trade name) for the treatment of hemophilia A (congenital Factor VIII deficiency). This product is similar in manufacturing to the other antihemophilic factor products manufactured by Bayer for the treatment of the same condition; the approved products include Kogenate/Kogenate-FS and Kovaltry. The new product, Jivi, is manufactured by Bayer Healthcare LLC at their campus in (b) (4) The product is supplied as a lyophilized powder and requires reconstitution with sterile water for injection for administration (same as for Kogenate/Kogenate-FS and Kovaltry). The diluent is supplied by two manufacturers, (b) (4) Bayer (b) (4).

The following information summarizes key background information pertaining to the new product, Jivi.

Drug Product Names

The following names are used to reference the drug product in this memo and in the BLA.

International Nonproprietary Name (INN): Damoctocog alfa pegol
Product Code: BAY 94-9027
Established Name: Antihemophilic Factor (Recombinant), PEGylated
Proprietary Name: Jivi

Chemical Structure
BAY94-9027 is a recombinant (r) B-domain deleted (BDD) human coagulation Factor VIII (FVIII) variant, which is site-specifically conjugated with a 60 kDa branched polyethylene glycol (PEG) molecule.

The BDD rFVIII variant contains (b) (4) A3, (b) (4) regions. The BDD rFVIII variant carries a point cysteine mutation in the A3 domain. The BDD rFVIII variant is secreted from the recombinant production cell line as a (b) (4) and BAY 94-9027 is produced by site specific conjugation of a single 60 kDa maleimide-derivatized PEG at the engineered cysteinyl residue.

Mode of Action
The PEGylated rFVIII product BAY 94-9027 temporarily replaces the missing coagulation Factor VIII needed for effective hemostasis in hemophilia A patients. BAY 94-9027 exhibits an extended terminal half-life (t1/2) and increased area under the curve through PEGylation compared to the un-modified recombinant Factor VIII product KOGENATE. PEGylation in the A3 domain reduces clearance of Factor VIII while maintaining the normal functions of the BDD FVIII molecule.

Proposed Clinical 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

The drug product, Damoctocog alfa pegol, is not indicated for the treatment of von Willebrand disease.

Dosage Form & Route of Administration
The BAY 94-9027 drug product is supplied as a lyophilized powder which requires reconstitution and is considered a parenteral solution. The drug product, BAY 94-9027, is 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). A vial adapter is included in the final packaging for facilitation with reconstitution and the final package also includes an administration kit for intravenous injection of the drug product.

Note, administrative connections supplied with the drug product are the same connections as supplied with Kogenate-FS and Kovaltry and are 510(k) approved. During the pre-BLA meeting, OTAT and CDRH discussed the need to re-review the information for Jivi and CDRH indicated the administration kits are the same along with the human factors study and thus a review of the same information

regarding the administration kits would not be necessary for this BLA. OTAT is responsible for reviewing the compatibility of the new drug product, Jivi, with the administration kits.

DMPQ elected to waive all inspections for this BLA as the Bayer site in (b) (4) Bayer (b) (4) were all recently inspected (recent meaning within the last 2 years) and all had good compliance records. The inspection waivers can be located in the EDR of the BLA. Further details on the manufacturing sites can be referenced in the "Manufacturing Sites for Jivi and Sterile Diluent" section of the memo.

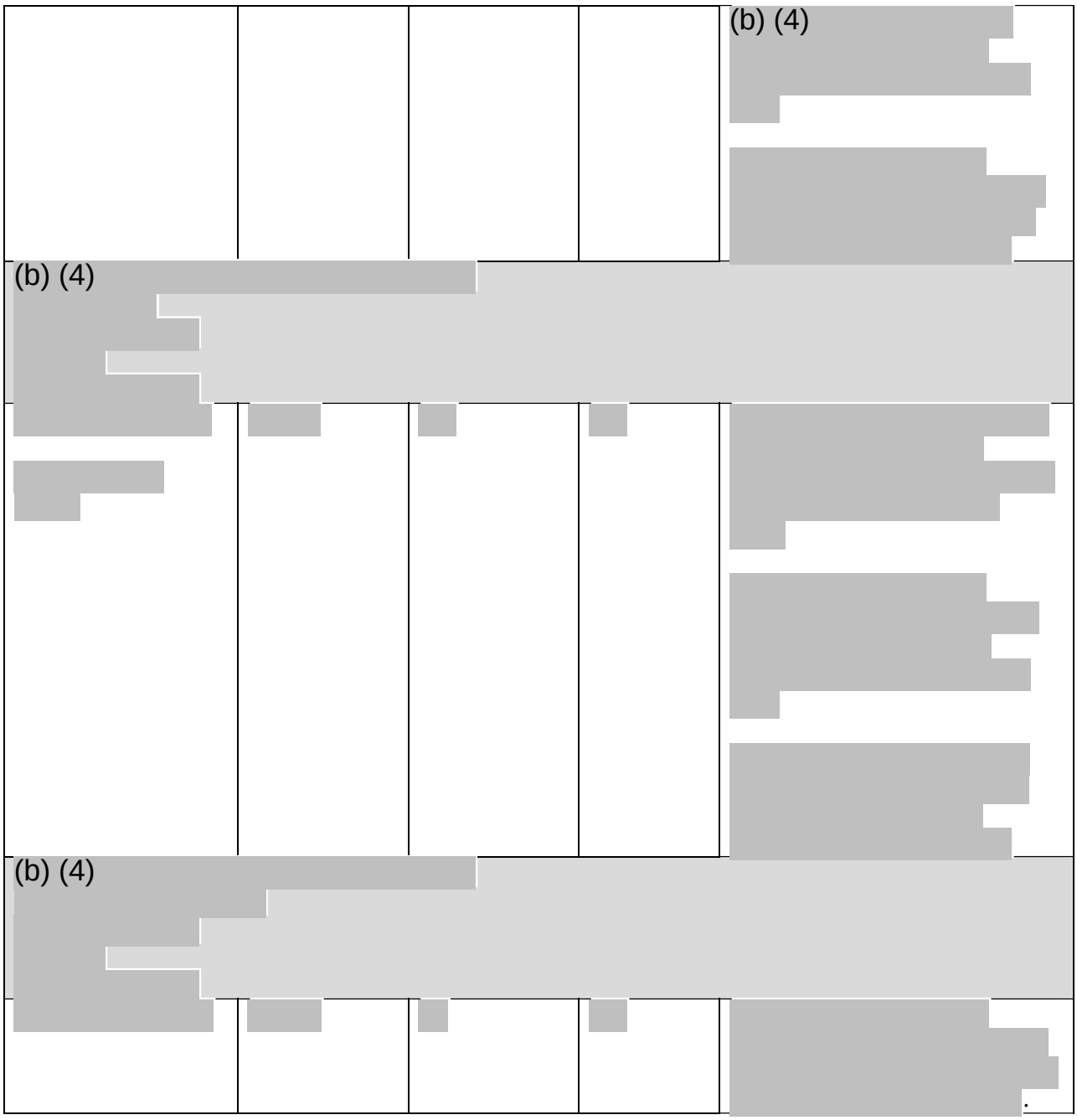
MANUFACTURING SITES FOR JIVI AND STERILE DILUENTS

The following is a summary of the responsible manufacturers and the facility sites where production activities occur related to the manufacture of Jivi and the sterile diluent.

Manufacturing / Testing Activities	**Inspection? Waiver? Not required?**	**Compliance Check required for approval?**	**RMS-BLA entry required?**	**Comments**
Bayer Healthcare LLC (b) (4)				
1) Drug substance, bulk drug product, and drug product manufacture 2) Primary and secondary packaging and labeling of drug product 3) QC release and stability testing of DS and DP 4) QA release of DS and DP 5) Stability testing of (b) (4) manufactured sWFI diluent (b) (4) 6) Storage of (b) (4) (b) (4) DP	Waiver	Yes	Yes	Licensed facility # (b) (4) Two recent inspections at Bayer Healthcare LLC support decision to waive inspection under this BLA: 1) Surveillance inspection conducted by Team Biologics (b) (4). A 23-item 483 was issued; inspection classified as VAI. 2) Surveillance inspection conducted by (b) (4) Inspection covered manufacturing areas for both Kogenate and Kovaltry. All systems covered during inspection including: quality, facility and equipment, materials, production, packaging and labeling, and laboratory. Inspection also reviewed corrective actions to Team Biologics inspection and determined actions adequate. No

				repeat observations were noted. A 2-item 483 was issued; inspection classified as VAI.
Bayer Healthcare LLC (b) (4)				
1) QC release and stability testing of DS and DP	Waiver	Yes	Yes	Note, this site is noted as Building (b) (4) by Bayer in the BLA and is used for QC testing. This building is included in the FEI # for the (b) (4) site. The (b) (4) inspection conducted in (b) (4) included this site/building (See note above)
Bayer Healthcare LLC (b) (4)				
1) Warehouse and distribution of finished Jivi market packages	Not required	No	Yes	
(b) (4)				
Bayer (b) (4)				
Sterile Water for Injection Diluent Manufacturer (Pre-filled Syringe) 1) Manufacturing and QC release and stability testing of diluent 2) Bulk packaging	Waiver	Yes	Yes	Two recent inspections at Bayer (b) (4) support decision to waive inspection under this BLA: 1) Surveillance inspection performed (b) (4) by IOG for CDER products including a (b) (4) No 483 was issued; inspection classified as NAI.

and labeling of Bayer (b) (4) manufactured diluent and of (b) (4) manufactured diluent 3) Storage and QA release for final packaging of Bayer manufactured and (b) (4) manufactured diluents				2) CDER NDA PAI performed (b) (4) by IOG. A 2-item 483 was issued. (decision and inspection not complete yet per FACTS and OSAR databases)
(b) (4)				
(b) (4)				



DRUG SUBSTANCE (JIVI)

The drug substance for Jivi is produced at Bayer's facility in (b) (4). The drug substance process includes the following steps: (b) (4) filtration. Each process step is described in further detail in the sections below. The following items related to the process and equipment will be described in this section, including: process description, raw materials, process validation, lifetime resin studies, container closure, stability, equipment description, equipment qualification, and equipment cleaning validation. The following sections in the drug substance section are the responsibility of OTAT to review as noted in the BLA table of contents at the top of the review memo.

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

(b) (4)

DRUG PRODUCT (JIVI)

The Jivi drug product will be produced in the same building on the (b) (4) Sterile Fill & Finish, using the same approved equipment as used for fill/finish activities for Kogenate-FS and Kovaltry and use the same aseptic processes and operations. No new equipment is required for the drug product process of Jivi as all existing equipment used for Kogenate-FS and Kovaltry will be used.

The Jivi drug product is produced in the following dosages: (b) (4), 500, 1000, 2000, and 3000 IU/vial. The nominal fill size is 2.5mL (target fill weight of (b) (4) for each dosage. The formulation excipient composition is the same between Bayer's recombinant Factor VIII products.

The container/closure configuration for the drug product is a 10 mL colorless glass Type I siliconized vial with bromobutyl gray type I stopper for lyophilization. The same vial/stopper combination is used for Kogenate-FS and Kovaltry. The reconstitution diluent is sterile water for injection. Note, the sterile water for injection will be covered in a separate section of this memo.

This section of the memo will contain information on the manufacturing process including process development and process description; critical process parameters for the drug product; process validation; drug product release specifications and batch analyses; drug product equipment summary, equipment qualification, and equipment cleaning validation; and drug product primary packaging information including container closure integrity.

DRUG PRODUCT MANUFACTURING PROCESS DESCRIPTION

The Jivi drug product manufacturing process involves (b) (4) sterile filtration, filling into vials, lyophilization, capping, visual inspection, and packaging. Each process step is described in further detail in the sections below.

Process Development

Bayer explains that the Jivi drug product manufacturing process was based on the commercial rFVIII Drug Product (Kovaltry) manufacturing processes for 2.5 mL fill size with the following modifications.

- The Damoctocog Alfa Pegol Drug Substance is (b) (4)
- For Damoctocog Alfa Pegol, all dosage strengths (b) (4) - 3000 IU/vial) are produced with 2.5 mL fill size, whereas for the commercial rFVIII processes there are two fill sizes, 2.5 mL (for (b) (4) 1000 IU/vial), and 5.0 mL (for 2000 IU/vial and 3000 IU/vial).
- The Damoctocog Alfa Pegol manufacturing process for 3000 IU/vial dosage (b) (4)
- For Damoctocog Alfa Pegol Polysorbate 80 is (b) (4) as for the Kogenate-FS process. This simplifies the Damoctocog Alfa Pegol Drug Product manufacturing process by (b) (4)

*Note, these changes for the Jivi drug product process were included in the process validation.

The freeze-drying process was established based on the Bayer's commercial rFVIII process for 2.5 mL fill size and has been demonstrated to be suitable and robust for freeze-drying Damoctocog Alfa Pegol Drug Product.

No changes were made in the manufacturing process, facilities and equipment between Phase 3 clinical batches and conformance batches. Bayer concludes that the batch analysis results from the Phase 3 clinical batches demonstrate that the Drug Product manufacturing process is reproducible and able to consistently produce Damoctocog Alfa Pegol Drug Product that meets the required specifications for clinical and conformance batches.

Drug Product Process Description

The following is a description of the bulking and filling process of the drug product for Jivi. Note, this process is (b) (4) to the processes for Kogenate-FS and Kovaltry as noted in the section above.

(b) (4) .

(b) (4)

Each vial of product is crimped with an aluminum seal with plastic flip-off top under controlled aseptic conditions.

After the vials are lyophilized, a (b) (4) is performed to ensure the correct appearance of the lyophilized drug product (i.e. cake appearance). Also, a (b) (4) is performed to ensure container closure integrity where the (b) (4) is measured. The vials are labeled and are then packaged into the final market packages and stored at 2-8°C in the warehouse.

CRITICAL PROCESS PARAMETERS

This section provides a summary of the critical process parameters in the Jivi drug product process.

The critical process parameter limits for the drug product are the listed in the following table below.

(b) (4)

(b) (4)

The maximum processing times for the drug product are listed in the table below.

(b) (4)

(b) (4)

The following table summarizes the critical process parameters for the lyophilization process step of the 2.5 mL vial size of Jivi.

(b) (4)

(b) (4)

The freeze dryer load size for the 2.5 mL fill size is between (b) (4) vials.

The following are the process parameter attributes for the bulking and filling steps.

(b) (4)

(b) (4)

(b) (4)

PROCESS VALIDATION

The purpose of the process validation was to provide documented evidence that the drug product manufacturing process can perform effectively and reproducibly to produce a product that meets the specifications and quality attributes. The drug product processes that were included in the validation

include: final bulk formulation, filling, freeze-drying, and vial capping. Two summary reports of the PV were provided in the BLA: one report for the bulking/filling steps and one report for the freeze-drying and vial capping processes; a summary of each report is detailed below.

The drug product process validation strategy included a (b) (4) approach for (b) (4) The executed process validation challenged the (b) (4) target batch sizes for the Damoctocog Alfa Pegol drug product at the (b) (4) dosages; therefore, Bayer concludes that this (b) (4) all Jivi dosages of (b) (4) 500, 1000, 2000 and 3000 IU. Drug product vials from the conformance batches were included in a stability program based on ICH guidelines to support shelf life assignment. Note, the review of the stability program and shelf life data is the responsibility of OTAT to review. It is noted that endotoxin (b) (4) and sterility (must comply meaning (b) (4) are parameters tested during the stability monitoring program for Jivi. Testing occurs at time = 0, 3 (b) (4) 6, 9, 12, 15, 18, and 24 months.

All conformance batches were filled into the proposed commercial primary packaging system (10 mL colorless glass type I siliconized glass vial with bromobutyl gray stopper for lyophilization). The following table summarizes the (b) (4) valid conformance runs that were executed across all dosage strengths and load sizes.

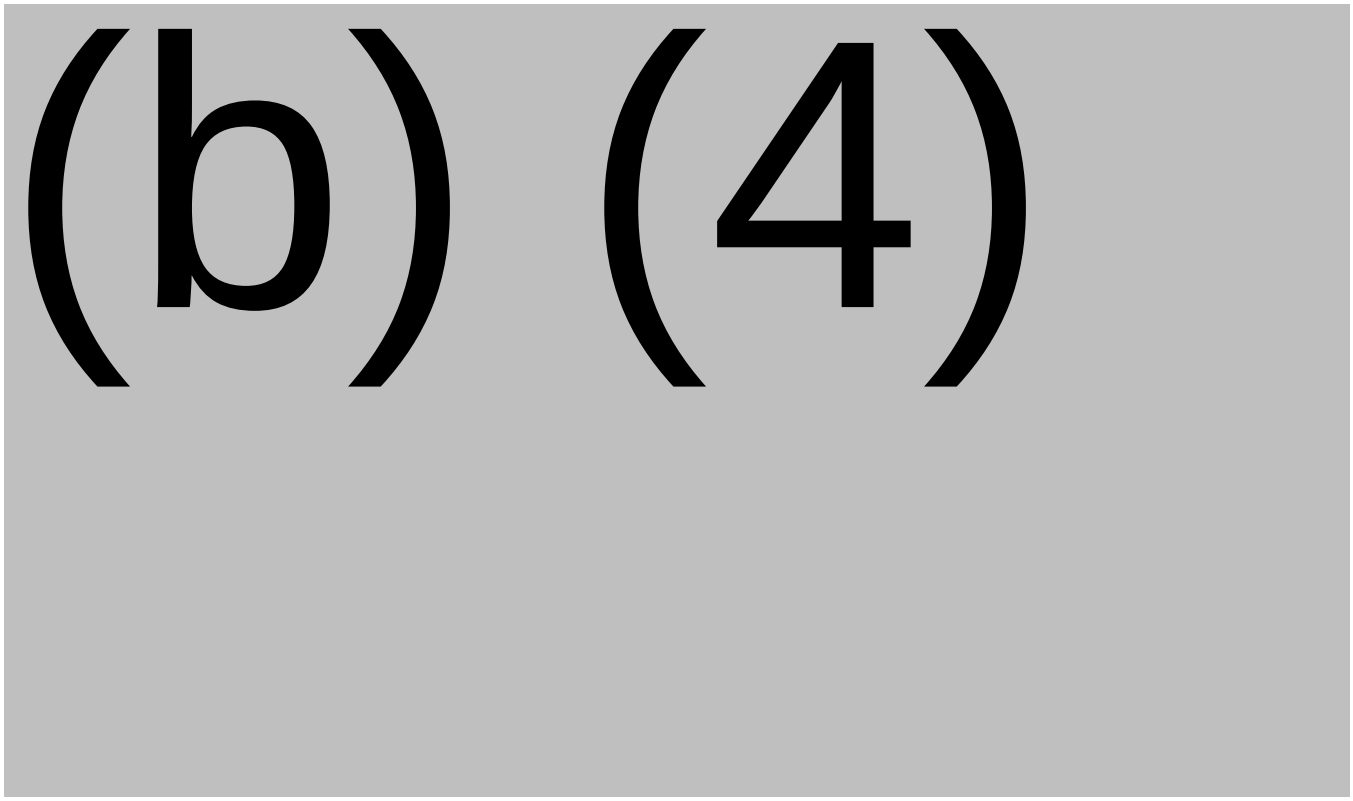
(b) (4)

(b) (4)

(b) (4)

Note, the number of runs completed for each dosage strength along with the lot size for the associated dosage is the responsibility of OTAT to assess if there are sufficient results from each dosage to demonstrate adequate process validation.

The following table summarizes the drug substance lots that were further processed into the drug product and represent the conformance lots for the drug product process validation.



Reviewer Comment: In the PV summary report for the Freeze-Drying and Capping processes, Bayer notes a deviation for Drug Product batch (b) (4) (noted in red in the above table 5th row) which ultimately lead to this batch being rejected. During drug product release testing of this batch, one vial measured a potency above the upper specification limit of (b) (4) (result was (b) (4) and this was considered out of the specification leading to the rejection of the batch. Bayer defends that this instance does not indicate that the processes, procedures, or equipment could not reliably and reproducibly produce a drug product that conforms to specifications, in-process controls, and quality requirements. To support this claim, Bayer notes they have manufactured (b) (4) conformance lots successfully and (b) (4) clinical batches at the 1000 IU dosage without failure. However, in order to show successful process capability of the 1000 IU dosage, (b) (4) additional conformance runs of the (b) (4) dosage were performed (specifically drug product lot numbers: (b) (4) , (b) (4) (b) (4) The strategy to manufacture (b) (4) conformance lots of the 1000 IU dosage in replacement of the single conformance run appears satisfactory to demonstrate the process capability; however, final determination regarding this approach is deferred to OTAT.

The following sections will describe the process validation that was performed for each segment of the drug product manufacture.

Process Validation: Bulking and Filling Process Steps
The purpose of the process validation is to demonstrate that the final bulk formulation and filling processes for Jivi can be maintained within established performance parameters and consistently produces a drug product which meets in-process acceptance criteria and release specifications.

From the review of the data,(b) (4) process validation lots, drug product lot nos. (b) (4) (noted in bold in Conformance Lot table above), were used to validate the max(b) (4) of the preparation of the (b) (4) . These lots were selected because they include the (b) (4) dosage forms (b) (4) The criteria for these steps are listed below along with the duration exceeded in the validation.

(b) (4)

The critical and key process parameter results of the bulk/filling process steps were provided in the summary report. Of the critical process parameters, DMPQ reviewed the results of the (b) (4) . All (b) (4) measures from each drug product lot were within the range indicated. As noted in the table above, the (b) (4) was exceeded for lots (b) (4) . The key process parameter table provided in the summary identified the criteria for the drug substance (b) (4) The durations for the (b) (4) noted steps were provided in the table above.

In the summary report, Table 3-4 was provided which lists the critical process performance attributes for the drug product lots. DMPQ reviewed the following results and confirmed the results met the criteria:

(b) (4)

The PV summary report for bulking/filling process steps also included the results of the drug product quality attributes for lots (b) (4) where the (b) (4) were exceeded. DMPQ reviewed the sterility and endotoxin results. Sterility was noted to comply. The criteria is “no

microbial growth (b) (4) . The endotoxin results for these lots met the criteria of (b) (4) . With the product results meeting the criteria, the results support the (b) (4) durations noted in the validation. The durations do not appear to have an impact on the quality of the product; however, final product quality determination is the responsibility of OTAT to assess.

The report also contained an evaluation of the (b) (4) ; this study is the responsibility of OTAT to assess.

Based on the outcomes of the testing and process parameter evaluation, Bayer concludes that the conformance batches demonstrate the robustness and consistency of the final bulk formulation and filling processes.

Reviewer Comment: Based upon the review of the (b) (4) results as measured from in-process tests (process performance attributes) or the finished drug product quality attributes, the results met the criteria indicating the process is capable of producing a sterile drug product. (b) (4) were also manufactured at durations which exceeded the maximum time limits for the respective process steps; the (b) (4) results from these lots also met the criteria indicating the process is effective and the product is not impacted. Based on the results of the bulking/filling process validation, DMPQ concurs that the processes have been adequately demonstrated and are considered validated. Final determination regarding the adequacy of the process validation is deferred to OTAT.

(b) (4)

(b) (4)

Media Fills

The Jivi drug product is manufactured in the same facility, Building (b) (4), using the same equipment as used for the approved products of Kogenate-FS and Kovaltry; therefore, the media fills are applicable and cover all three products.

To validate the aseptic process, (b) (4) media fills were performed with (b) (4) vials, respectively. The vials were (b) (4) The media fills were performed under (b) (4) The acceptance criteria are the following:

(b) (4)

The media fills consisted of (b) (4) media fills met the acceptance criteria. After the initial validation, media fills in the filling facility are performed (b) (4) to requalify the facility.

Reviewer Comment: The information on the media fills is not clear as it is not understood if the (b) (4) media fills support the initial qualification/validation of the aseptic operations of the manufacturing process or if the media fills were performed in support of Jivi drug product manufacturing; therefore, Bayer is asked to clarify. Also, since Bayer performs a (b) (4) media fill, I am requesting the data from the most recent media fill to review as confirmation of their aseptic operations.

Information Request #1, Question #2: Regarding your media fill results that were provided in Process Validation – Bulking/Filling dossier (page 25/25, section 5.2 Aseptic Filling (Media Fills)), please

clarify the dates in which the media fills were performed. The information provided does not clearly explain if the media fills were performed to demonstrate the aseptic operations of the Jivi drug product or if the media fills were performed as part of the validation for the commercial facility operations for Kogenate-FS. Please clarify.

Bayer Response (Amendment #26): The initial media fills were performed on (b) (4) as part of the validation for the commercial facility operations for Kogenate-FS (Antihemophilic Factor (recombinant) Formulated with Sucrose). The Jivi (Damoctocog Alfa Pegol) drug product is aseptically filled in the licensed commercial fill facility using the same utilities, equipment, process and personnel used to manufacture Bayer's currently marketed Antihemophilic Factor (recombinant) Formulated with Sucrose and Kovaltry rFVIII drug products. Therefore, media fills performed to document that the aseptic filling process is in a state of control are applicable to all rFVIII products filled at the (b) (4) sterile fill facility, including Damoctocog Alfa Pegol.

Reviewer Response: The response by Bayer clarifies that the media fill information provided in the BLA is from the original validation of the facility for Kogenate-FS. The media fill information does show the aseptic conditions used to sterile filter and fill Kogenate-FS is in a state of control; it is not representative of the current state of the facility. DMPQ requested the results of the most recent media fill which covers the Jivi product as Bayer explains that all three rFVIII products are covered in the same media fill as the same equipment, process, facility, utilities, and personnel are used to manufacture the three rFVIII products (see IR #1, Question #3 below for request).

Information Request #1, Question #3: Please provide a summary report of your most recent media fill supporting the aseptic manufacturing process for Jivi. At a minimum, please include the number of vials filled, acceptance criteria, results, summary of the interventions that were performed, duration of media fill, and explain if the media fill covers change of personnel.

Bayer Response (Amendment #26): A summary of the two most recent media fills performed in (b) (4) to support the aseptic manufacturing process for Jivi (Damoctocog Alfa Pegol), including the number of vials filled, acceptance criteria, results, summary of the interventions performed, duration of media fill and the change of personnel during the aseptic process simulation, are presented in Process Validation and/or Evaluation – Media Fills (P.3.5.50#016697459-01).

Reviewer Comment: Bayer provided the requested information from the most recent media fill supporting the Jivi manufacturing process. DMPQ reviewed the updated Process Validation and/or Evaluation – Media Fill Report (Report #016697459-01) as provided by Bayer in this amendment.

The report explained that the media fills performed cover all three rFVIII products filled in the (b) (4) Sterile Fill Facility, including Jivi. The most recent (b) (4) media fills were performed on (b) (4) each with not less than (NLT) (b) (4) vials, which were filled and loaded within a time duration that represents a (b) (4) load size operation. The media fills followed routine process activities and incorporated planned interventions that were representative of interventions that might occur on the filling line during routine drug product manufacturing in order to challenge and assess the state of aseptic process control. All authorized personnel who enter the aseptic processing areas during production participated in the media fills and the aseptic process simulation includes a

change of personnel. A summary of the filling interventions as performed during the media fills was provided in Table 3-1 of the response. The interventions are typical of situations that could possibly occur during a media fill such as: (b) (4) . Bayer provided a summary of the results of the (b) (4) media fills from (b) (4) as noted and (b) (4) passed without any contaminated vials. The results demonstrate that the filling processes produces a sterile product and has been successfully re-validated. No review issues are noted regarding the media fills in support of the Jivi drug product manufacturing process.

Process Validation: Freeze Drying and Vial Capping Process Steps
The purpose of this process validation is to demonstrate that the Freeze-Drying and Vial Capping processes for Jivi can be maintained within established operational process parameters and that a drug product can be consistently produced which meets in-process acceptance criteria and release specifications. The same conformance lots which were listed in the table above were further processed through the freeze drying step and then capped to produce the final drug product presentation.

The number of vials which were freeze dried for each drug product batch are identified in the above table. The quantity of vials freeze dried included the (b) (4) number of vials (range (b) (4) vials).

The validation summary contained a table showing the results of the critical process parameters that were monitored during freeze-drying operations for each of the drug product lots. The process parameters evaluated included (b) (4) during the (b) (4) . All lots were within the criteria.

Included in the validation report was a summary table showing the drug product quality attribute test results for each conformance lot (these tests and criteria are release tests for the drug product – refer to table "Jivi Drug Product Release Specifications" below). DMPQ reviewed the following results: moisture, endotoxin, and sterility. The moisture results from each lot were below the (b) (4) criteria. The endotoxin results were all below the criteria of (b) (4) . The sterility results were all noted to "comply" meaning no microbial growth observed (b) (4) The remaining test results are deferred to OTAT for review and evaluation. It is noted there was one deviation due to the rejection of 1000 IU dosage drug product batch (b) (4) due to out-of-specification of the potency result exceeding the maximum limit. This batch was rejected due to the result and Bayer manufactured (b) (4) conformance batches of the 1000 IU dosage in replacement. DMPQ does not have any issues with the sterility, endotoxin, or moisture results of the 1000 IU dosage conformance batches (lots (b) (4) , (b) (4) which were manufactured to demonstrate the capability of the process to produce a reliable and consistent 1000 IU dosage drug product. However, final determination regarding the outcomes and results of the product results is deferred to OTAT.

As part of the process validation, Bayer selected (b) (4) batches of the conformance lots to demonstrate process uniformity and reproducibility. The drug product lot numbers included in the study are the following: Lot No. (b) (4) The lots were selected to

(b) (4)
. Drug product samples taken from (b) (4)
of the freeze-dryer were tested for (b) (4)
in the freeze dryer. For the (b) (4)
.

The test results for (b) (4)
lots sampled were provided in the PV summary report. The results met the specifications (specifications noted in table "Jivi Drug Product Release Specifications" below).

As part of the uniformity and reproducibility study, Bayer analyzed the (b) (4)
product test results between (b) (4) and generated graphs to show the uniformity of the results. The graphs show the results are consistent between the (b) (4) within the lot and are similar across the (b) (4) lots evaluated. DMPQ has no issues with the uniformity analysis; however, final determination and review of the data/graphs is deferred to OTAT.

Bayer concludes that the process validation results from the conformance runs indicate that the freeze-drying cycle is capable of producing Damoctocog Alfa Pegol Drug Product meeting the quality attribute specifications.

Reviewer Comment: Based on the results of the process validation for the bulking/filling and freeze-drying and vial capping processes, the results demonstrate the Jivi drug product can be manufactured under aseptic conditions and produce a product that meets the sterility, endotoxin, and moisture specifications of the finished drug product. In addition, the results of the process mapping uniformity study show that the product results are consistent and uniform across all sampled (b) (4) locations of the freeze-dryer. DMPQ does not have any issues with the process validation of the drug product. Final determination of the drug product process validation and drug product results are deferred to OTAT.

DRUG PRODUCT SPECIFICATIONS & BATCH ANALYSES

The following table provides a summary of the drug product release specifications for Jivi. Note, the potency is dependent upon the final target of the product dosage. The table shows a range which covers the product potency from (b) (4) IU to 3000 IU.

Jivi Drug Product Release Specifications

Parameters	Analytical Method	Specification
Physical and Chemical	Appearance before reconstitution	White to slightly yellow solid
	Appearance after reconstitution	Clear, colorless liquid, Free of visible particles
	Clarity	(b) (4)
	Color	(b) (4)
	Solubility time	(b) (4)
	pH	6.6 – 7.0
	(b) (4)	

	Moisture	(b) (4)
	Particulate Matter Number of particles per vial (b) (4)	(b) (4)
	Particulate Matter Number of particles per vial (b) (4)	(b) (4)
	(b) (4)	Must comply (b) (4)
Identity	Identity (b) (4))	Must Comply (b) (4)
Purity/Impurities	Purity: (b) (4) (b) (4)	
	(b) (4)	
	(b) (4)	
Potency	Chromogenic assay: Potency (b) (4) IU 500 IU 1000 IU 2000 IU 3000 IU	(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)
	Chromogenic assay: Potency (b) (4) 500 IU 1000 IU 2000 IU 3000 IU	(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)
	Specific Activity (Chromogenic assay (b) (4)	(b) (4)
	Total Protein (vial): (b) (4) IU 500 IU	(b) (4) (b) (4)

	1000 IU	(b) (4)
	2000 IU	
	3000 IU	
	Total Protein (b) (4) IU	(b) (4)
	500 IU	
	1000 IU	
	2000 IU	
	3000 IU	
Safety	Sterility	Must comply (no microbial growth (b) (4)
	Endotoxin (b) (4))	(b) (4)
Excipients	Glycine	(b) (4)
	Sodium	(b) (4)
	Calcium	(b) (4)
	Histidine	(b) (4)
	Sucrose	(b) (4)
	Polysorbate 80	(b) (4)

In Section 3.2.P.5.4 Batch Analyses, Bayer provided the results of the drug product lots that were manufactured for the process validation. The results were compared to the drug product specifications, listed in the table above. DMPQ is responsible to review the endotoxin and sterility results of the batches. The following batches were provided in the batch analyses.

(b) (4) IU dosage: Batches (b) (4)
The endotoxin and sterility results for these (b) (4) batches met the specification.

500 IU dosage: Batch (b) (4)
The endotoxin and sterility result for this batch met the specification.

1000 IU dosage: Batches (b) (4)
The endotoxin and sterility results for these batches met the specification.
Note, the final drug product release results for IU dosage lot (b) (4) were not included in the Batch Analyses as this lot was rejected as noted in the Drug Product Process Validation section of the memo.

2000 IU: Batch (b) (4)
The endotoxin and sterility results for these (b) (4) batches met the specification.

3000 IU: Batches (b) (4)
The endotoxin and sterility results for these batches met the specification.

SUMMARY OF DRUG PRODUCT EQUIPMENT, EQUIPMENT QUALIFICATION, & CLEANING VALIDATION

The following is a summary of the manufacturing equipment which is used in the manufacture of the drug product of Jivi at the Bayer (b) (4) facility in Building (b) (4) Sterile Fill & Finish Facility. This section will also provide a summary description of the equipment qualification that was performed. Information pertaining to the cleaning of the equipment is also described in this section. Note, all equipment is multi-product use and is also used in the manufacture of Kogenate-FS and Kovaltry.

Reviewer Comment: As Bayer is using previously qualified equipment to manufacture the drug product of Jivi, the equipment qualifications of the drug product equipment were not reviewed in-depth for this BLA as the equipment qualification was previously reviewed during the review of Kogenate-FS and Kovaltry. Also, equipment maintenance and calibration are routinely reviewed during the surveillance inspection; the recent inspection in (b) (4) did not reveal systemic concerns related to equipment operation, maintenance, or calibration. Therefore, based on these elements, the equipment qualification for the drug product equipment will not be re-reviewed.

Regarding the cleaning of the shared equipment, the cleaning validation of the equipment soiled with Kovaltry was submitted with the Kovaltry BLA (STN 125574/0) for review. Bayer explains that the cleaning validation was performed concurrently on the shared equipment used for both Kovaltry and clinical lots of Jivi. Bayer indicates that the equipment cleaning procedures were successfully qualified for use on the shared equipment soiled during the manufacture of Kovaltry or Jivi (clinical). Note, While the cleaning validation for equipment soiled with Kovaltry was reviewed under STN 125574/0, Bayer will need to provide data showing the removal of Jivi from the shared surfaces.

The following sections summarize the major pieces of equipment that are used in the drug product manufacturing process of Jivi. Reminder, all drug product equipment is shared between Kogenate-FS, Kovaltry, and Jivi. Specific equipment details pertinent to the shared usage between the three products will be noted below if warranted.

(b) (4) ***Bulking Equipment***

(b) (4)

(b) (4)

Equipment Qualification
The qualification of the (b) (4) included verifying operation of the (b) (4) .

Reviewer Comment: As the (b) (4) are pre-existing and shared amongst the three products, the review of the qualification information is not warranted for this BLA. (b) (4) studies involving the (b) (4) were included in the PV reports and are the responsibility of OTAT to assess. The results of the drug product final release results support the intended use of the equipment.

Cleaning Validation
The cleaning and sterilization of the (b) (4) was qualified utilizing (b) (4) systems. (b) (4) were used for sterilization qualification to show acceptable(b) (4) and to verify reduction in viable organisms.

Reviewer Comment: As (b) (4) are used to (b) (4) (b) (4) and are shared amongst the three products, I am requesting additional clarification from Bayer to show they have effectively removed the Jivi product from the (b) (4) to mitigate cross-contamination concerns.

Information Request #1, Question #4: Please provide summary information and clarification regarding the cleaning process and validation for the (b) (4) which are used in the manufacture of Jivi in process steps such as the (b) (4) . Please indicate if a cleaning validation or verification was performed of the (b) (4) following (b) (4) with Jivi and if so, please provide the criteria and results.

Bayer Response (Amendment #26): Cleaning validation of the (b) (4) used in the Jivi (Damoctocog Alfa Pegol) drug product manufacturing process was performed by (b) (4) Test results and acceptance criteria for the cleaning validation runs for the equipment are presented in Qualification/Validation of Bulking/Filling Equipment (Report 016697456).

Reviewer Response: Bayer indicated they have (b) (4) with the Jivi drug product and performed a cleaning validation following this (b) (4) . The report (report no. 016697456) was provided by Bayer in the response and reviewed by DMPQ. Pertinent information from the report regarding the cleaning of the (b) (4) with Jivi drug product are noted below.

In the report, Bayer explains the (b) (4) are cleaned (b) (4) .

The validation established (b) (4)

(b) (4)

The following are the criteria used to establish the clean equipment hold time:

(b) (4)

The results for (b) (4) were below the criteria.

Overall, the results were provided and compared to the acceptance criteria; the results met the criteria thereby demonstrating the cleaning method is acceptable to remove the soilant, Jivi, from the shared (b) (4)

Bayer has provided acceptable information demonstrating the cleaning method is acceptable to remove the drug product, Jivi, (b) (4) . No further review of the cleaning method of the shared (b) (4) is necessary.

Vial Preparation

- (b) (4) .

Equipment Qualification

(b) (4) .

Cleaning Validation

(b) (4) .

- (b) (4)

Equipment Qualification
(b) (4)

Reviewer Comment: As the same qualified equipment is used for vial preparation, DMPQ did not perform a review of the (b) (4) as this equipment was previously qualified for Kogenate-FS. The equipment is shared between Kogeante-FS, Kovaltry, and Jivi products and all three products are filled into the (b) (4) . As the equipment are pre-existing and multi-use, the re-qualification of the equipment along with the calibration and maintenance are reviewed during routine surveillance inspections.

Filling Equipment

- Vial Filling/Stoppering Machine: The filling/stoppering machine is located in a (b) (4) .

Equipment Qualification
Filling equipment was qualified and tested for proper movement of vials through the filling equipment and proper filling of product into vials.

Reviewer Comment: The filling equipment used for the filling of Jivi is the same as used for Kogenate-FS and Kovaltry and has been previously qualified for use. The maintenance of the equipment is routinely reviewed during the surveillance inspections. For the drug product process validation, (b) (4) conformance lots were filled using the filling equipment. As part of the validation, (b) (4) . Additionally, the 2.5mL vial size is universal between all three products. Based on these rationales, a review of the equipment qualification for the filling/stoppering machine is not warranted for this BLA. No issues are noted regarding the filling equipment.

Cleaning Validation
Cleaning and sterilization cycles were qualified utilizing (b) (4) systems that are qualified in the production areas. Cycles were defined and qualified to ensure sterility of the filling equipment. (b) (4) to verify acceptable reduction in viable organisms.

Reviewer Comment: Although the filling equipment is shared between the three antihemophilic factor products, Bayer has not provided sufficient information to determine the adequacy of the cleaning of the filling equipment product contact surfaces in this BLA for Jivi. It is assumed that

the cleaning process is the same for all three products as they have similar product characteristics; however, this information was not discussed in the BLA. Information regarding the cleaning cycle and the comparability of the (b) (4) is requested. Also, Bayer is requested to provide a summary of the most recent re-qualification of the sterilization process for the filling equipment in order to confirm the adequacy of the cycle.

Information Request #1, Question #5: Regarding the filling product contact parts including the (b) (4) please clarify if the product contact parts are dedicated to Jivi, shared, or single-use disposable. If shared, please identify the other products. Please summarize the cleaning process of the filling product contact parts.

Bayer Response (Amendment #26): The following table was provided in the response listing the filling equipment and parts which are used in the filling of all three rFVIII drug products. The cleaning process for the product contact parts was also provided in the response in a separate table also provided below. Bayer explained the (b) (4) .

(b) (4)	

The following table summarizes the filling equipment parts cleaning cycles for product contact parts used in the filling of Jivi.

Equipment/Part	Cleaning Cycle
(b) (4)	

Reviewer Comment: Bayer has indicated they use shared (b) (4) for all three rFVIII products; therefore, additional information regarding the validation of the cleaning cycle of the (b) (4) is warranted along with information regarding the sterilization of the (b) (4) .

Information Request #5, Question #3: In your March 23, 2018 response to Question #5, you noted the (b) (4) are shared between all three rFVIII products. The response indicates there are (b) (4) You also indicate the (b) (4) are (b) (4) . Please address the following inquiries regarding the (b) (4) :

a. Please provide a summary of the cleaning validation that has been performed to demonstrate the effectiveness of the cleaning cycle to remove product residue from the (b) (4) . Please ensure your response include a summary of the (b) (4) samples that were analyzed.
b. Please provide a summary which demonstrates the effectiveness of the sterilization cycle to produce sterile (b) (4) .

Bayer Response (Amendment #48): The (b) (4)

Response to Part A: (b) (4) As described in our March 23, 2018 response to Question #5 in document Qualification/Validation of Bulking/Filling Equipment, the (b) (4) are cleaned with an (b) (4) .

Small parts, including the (b) (4) . These data are now included in the amended document Qualification/Validation of Bulking/Filling Equipment.

(b) (4)

Reviewer Comment: The response by Bayer to part A of this request is adequate as Bayer has provided a clear explanation of their cleaning process and has also provided a summary of their cleaning validation which included (b) (4) with the Jivi drug product. The results of the cleaning validation of the (b) (4) were shown to meet the criteria.

Response to Part B: (b) (4)

As summarized in document Qualification/Validation of Bulking/Filling Equipment, the (b) (4) requalification of the (b) (4) performed in (b) (4) consisted of (b) (4) , as presented in Table 3-2 and Table 3-3 of the response.

Reviewer Comment: The information provided in the response to part B regarding the validation of the (b) (4) is acceptable as Bayer provided the results and criteria from their latest (b) (4) requalification of the (b) (4) as performed in (b) (4). The results provided Tables 3-2 and 3-3 of the response met the criteria listed to demonstrate successful (b) (4) of the (b) (4). No further review issues remain regarding the (b) (4) of the (b) (4).

Information Request #1, Question #6: For the cleaning of the filling machine, please address the following:

a. Please explain if the cleaning cycle was changed due to the introduction of Jivi.

   Bayer Response (Amendment #26): The cleaning cycle was not changed due to the introduction of Jivi; the same utilities, equipment, process and personnel are used to manufacture Bayer's currently marketed rFVIII products. Cleaning development and validation studies demonstrated that all three rFVIII products have similar cleanability from equipment surfaces. Equipment soiled with rFVIII products are cleaned with (b) (4) . Non-product contact equipment (e.g. lyophilizers) are cleaned with (b) (4). The same cycles used for cleaning of equipment used in the Antihemophilic Factor (recombinant) Formulated with Sucrose (Kogenate-FS) and BAY 81-8973 (Kovaltry) processes were found to be adequate in ensuring equipment cleanliness when used on equipment used in the manufacture of Damoctocog Alfa Pegol.

b. Please indicate if a cleaning verification or validation of the filling equipment was performed using (b) (4). If so, please provide a summary of the cleaning validation along with the acceptance criteria and results.

   Bayer Response (Amendment #26): Cleaning validation of the filling equipment was performed using (b) (4). A summary of the cleaning validation, including acceptance criteria and results are presented in Qualification/Validation of Bulking/Filling Equipment (Report 016697456).

Reviewer Response: Bayer has provided an acceptable response explaining the three rFVIII products have a similar cleanability based on their development and validation studies of removing the materials from equipment surfaces. DMPQ performed a review of the cleaning validation of the filling equipment as provided in the Qualification/Validation of the Bulking/Filling Equipment in Report No. 016697456. A summary of the pertinent information from the report follows.

Per the report, the vial filling/stoppering machine is cleaned (b) (4) . The cleaning method was originally validated with (b) (4) This same cleaning method was confirmed to be acceptable with (b) (4) runs performed, using (b) (4) . The validation established (b) (4) . Effectiveness of the cleaning cycle to remove residues and cleaning agents to acceptable levels was demonstrated through analysis of (b) (4) . The criteria for the cleaning validation of the vial filling/stoppering machine are the following:

(b) (4)

The results were provided in comparison to the criteria and were shown to meet the criteria thereby demonstrating the cleaning process and method are applicable to remove traces of Jivi residue.

Reviewer Comment: The results demonstrate that the filling machine is adequately cleaned following (b) (4) drug product. The same cleaning cycle and method has been found acceptable for the other rFVIII products as well. No further issues remain regarding the cleaning of the filling machine.

Information Request #1, Question #7: Regarding the sterilization of the filling equipment used for Jivi, please provide a summary including criteria and results of your most recent re-qualification of this process.

Bayer Response (Amendment #26): A summary of results of the most recent requalification including acceptance criteria and results of the sterilization of the filling equipment is presented in Qualification/Validation of Bulking/Filling Equipment (Report 016697456).

Reviewer Comment: The results of the most recent requalification of the sterilization cycle in the vial filling/stoppering machine as noted in Report 016697456 were reviewed; a summary follows.

The (b) (4) requalification is based on the performance of (b) (4) for the Vial Filling/ Stoppering Machine. Requalification is performed utilizing (b) (4) for the Vial Filling/

Stoppering Machine, (b) (4)

The sterilization requalification results for the Vial Filling/Stoppering Machine performed in (b) (4) indicate that sufficient (b) (4) as demonstrated in Table 3–1 of the report and the results indicated that the (b) (4) sterilization of the filling/stoppering machine is effective.

No issues are noted in the review of the sterilization cycle requalification as performed in (b) (4).

Freeze-Drying Equipment

- Lyophilizers: (b) (4) lyophilizers are used to freeze-dry the product in vials and seat the stoppers under vacuum at the end of the freeze-drying cycle. The lyophilizers are equivalent in design, size, and operating principle, and are designed for (b) (4) he lyophilizers used for Jivi are unit numbers (b) (4). Note, the same lyo units are used for the freeze-drying of Kogenate-FS and Kovaltry.

  Equipment Qualification
  (b) (4)

  Information Request #1, Question #8: Regarding the freeze-drying process of Jivi, please explain if (b) (4) were performed for Jivi. (b) (4) studies were performed for Jivi, please provide a summary of the study including acceptance criteria and results. If the studies were not performed, please provide your justification.

  Bayer Response (Amendment #26): The Jivi drug product is aseptically filled using the same utilities, equipment and a very similar process used to manufacture Bayer's currently marketed rFVIII drug products (Kogenate-FS and Kovaltry). All three drug products have the same product formulation and fill volume, and utilize the same lyophilization cycles for freezing, (b) (4) are applicable to all rFVIII products, including Damoctocog Alfa Pegol.

  Reviewer Response: The response by Bayer explains that the same lyo cycle is applicable to all three rFVIII products; therefore, (b) (4) were not needed for the Jivi product because of the product similarities to the other two rFVIII products. The response is acceptable and no further review of the lyophilizer qualification or cycle studies are necessary.

Cleaning Validation
Cleaning and Sterilization cycles were qualified utilizing (b) (4) . Cycles were defined and qualified to ensure sterility of the lyophilizers following a lyophilization cycle (b) (4)

Information Request #1, Question #9: Regarding the cleaning and sterilization of the lyophilizers used for Jivi, please address the following requests:

a. Please explain if the (b) (4) were changed resulting from the introduction of Jivi. If so, please provide applicable requalification and/or revalidation summary reports.

Bayer Response (Amendment #26): No changes in the (b) (4) for the lyophilizers were made for introduction of Jivi, which uses the same utilities, equipment, process and personnel to manufacture Bayer's currently marketed Kogenate-FS and Kovaltry drug products. Cleaning development and validation studies demonstrated that all three rFVIII products have similar cleanability from equipment surfaces. The same cycles used for cleaning of the lyophilizers used in the commercial Kogenate-FS and Kovaltry processes were found to be adequate in ensuring equipment cleanliness when used on equipment used in the manufacture of Jivi.

No changes in the (b) (4) were made for introduction of Damoctocog Alfa Pegol, which uses the same lyophilizers to manufacture Bayer's currently marketed Kogenate-FS and Kovaltry drug products.

b. Please provide a summary of the cleaning validation or verification that was performed to demonstrate removal of Jivi residue.

Bayer Response (Amendment #26): A summary of the cleaning validation performed to demonstrate removal of Damoctocog alfa pegol residue is presented in Qualification/Validation of Bulking/Filling Equipment (Report 016697456).

c. Please provide a summary of the results of your most recent requalification of the (b) (4) applicable to Jivi manufacture.

Bayer Response (Amendment #26): A summary of results of the most recent requalification of the (b) (4) for the lyophilizers is presented in Qualification/Validation of Bulking/Filling Equipment (Report 016697456).

Reviewer Response: Bayer confirmed in their response that the (b) (4) in the lyophilizers were not modified based on the introduction of Jivi; Bayer has performed development and validation studies to confirm the soilant removal of the rFVIII products is similar and the cycles are adequate to remove the product materials. DMPQ performed a review of the cleaning validation summary and requalification of the (b) (4) as provided in the Qualification/Validation of Bulking/Filling Equipment (Report 016697456). A summary of the two studies follows.

Lyo Cleaning

Cleaning of the lyophilizers is accomplished through use of an (b) (4)

:

(b) (4)

The results were provided and confirmed to meet the criteria thereby demonstrating that the cleaning process and method is effective to remove the soilant, Jivi, from the surfaces of the lyophilizer.

The Clean Equipment (b) (4) was based on the Kogenate® product and is applicable to Jivi given that the cleaning process and method is the same and the products are similar soilants.

Lyo Sterilization

*Note, the original validation was performed in (b) (4) and has been re-qualified on (b) (4) basis since that time. For this review, only the results from the latest re-qualification will be reviewed.

The main phase of the (b) (4) requalification is based on the performance of (b) (4) sterilization run for each lyophilizer. Requalification is performed utilizing (b) (4)

The requalification follows the (b) (4)

(b) (4)
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The sterilization requalification results for the lyophilizers performed in (b) (4) as demonstrated in Table 3–2 and Table 3–3 of the report where the criteria were compared to the results (Note, each table contains the results from (b) (4)). The results indicated that the (b) (4) sterilization of the lyophilizers is effective.

Reviewer Comment: The results from the cleaning validation in which Jivi was used as the (b) (4) indicate the cleaning cycle is effective at removing residue from the lyo equipment surface. Also, the results from the latest requalification of the lyophilizer demonstrate the (b) (4) is effective. No further issues are noted regarding the use of the lyophilizer in the manufacture of Jivi.

Capping Equipment

- Automated capping equipment is used to apply an aluminum overseal or reconstitution cap to fully stoppered vials (note, Jivi will only be supplied using an aluminum overseal. Kogenate-FS and Kovaltry can be capped with an alternate seal, a reconstitution cap). Aluminum overseals are applied in (b) (4)

Equipment Qualification
Capping equipment was tested for proper movement of vials and capping after lyophilization.

Reviewer Comment: As the capping equipment is shared between the three products and all products are capped with an aluminum overseal, the review of the equipment qualification for this machine is not warranted under this BLA. The equipment maintenance of the capping machine is routinely reviewed during the surveillance inspections.

Process Support Equipment

(b) (4)

Equipment Qualification

(b) (4)
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Information Request #1, Question #10: Regarding the autoclave which is used to (b) (4) please confirm if there have been any changes to the qualified (b) (4) . If so, please provide a summary of the new (b) (4)

Bayer Response (Amendment #26): No changes in the product contact filling equipment qualified (b) (4) for the sterilization cycle were made for introduction of Jivi (Damoctocog Alfa Pegol), which uses the same filling equipment and sterilizers to manufacture Bayer's currently marketed rFVIII drug products Kogenate-FS and Kovaltry.

Reviewer Comment: As the (b) (4) have not changed due to the introduction of Jivi, the qualification of the autoclave did not require review.

(b) (4)

Packaging Equipment

- Packaging equipment was qualified and tested for proper movement of vials and packaging components through the packaging equipment and to ensure accurate and consistent operation within the design parameters.

Reviewer Comment: Albeit from some minor process differences, the drug product processes of Kogenate-FS, Kovaltry, and Jivi are (b) (4) The same facility and equipment are used to produce the three drug products of Kogenate-FS, Kovaltry, and Jivi. Based upon the information in the BLA and Amendments, DMPQ does not have any review issues with the drug product process validation, drug product equipment qualification, or drug product equipment cleaning validation.

CONTAINER CLOSURE (PRIMARY PACKAGING)

The container closure system for Jivi consists of a glass vial, stopper, and sealed with an aluminum seal and plastic flip top.

The container for Jivi is a 10mL glass vial with colorless glass, type I, and silica-coated. The vial is supplied by (b) (4) . The stopper is a gray bromobutyl rubber, silicone coated, suitable for lyophilization processes. The stopper is supplied by (b) (4) . The overseal is a lacquered aluminum seal with plastic flip-off top. Both vial and stopper are sterilized by Bayer. The vial neck and stopper are both 20 mm. The safety of the container closure system's materials of construction have been assessed by Bayer. This section will focus on the vial/stopper description and the container closure integrity testing of the vial/stopper.

Both Kogenate-FS and Kovaltry utilize the same primary packaging system as proposed for use with Jivi. The only difference is that both Kogenate-FS and Kovaltry can be alternately sealed with a reconstitution cap in additional to the aluminum seal. Also, both Kogenate-FS and Kovaltry have fill volumes of 2.5mL.

Bayer has performed container closure integrity testing along with compatibility studies and extractable studies to show the acceptability of the primary packaging with the Jivi drug product. DMPQ evaluated the container closure integrity testing results. OTAT is responsible to review the compatibility study and the extractable study.

Container Closure Integrity Testing

In order to demonstrate that the primary packaging provides protection from gas and water vapor permeation, (b) (4) have been performed. In addition, (b) (4) is performed as a shelf-life test. (b) (4) testing was performed to verify the container/closure seal when the aluminum cap is used. The results of the (b) (4) testing for the aluminum cap are described below.

The validation of the container/closure configuration was carried out with (b) (4)

(b) (4)

Reviewer Comment: The container closure method validation was reviewed under the Kovaltry BLA STN 125574/0 and was found to be acceptable. The method validation does not require review under this BLA. The results of the container closure integrity testing demonstrate the seal is adequate to

maintain a sterile finished drug product. No further issues are noted regarding container closure integrity testing.

Container Closure Functionality
Bayer has evaluated the container closure functionality by evaluating the (b) (4) required to combine the vial adapter with the container closure for the Jivi drug product. The acceptance criteria for the (b) (4) ". In the study, (b) (4) The study showed the vial adapter is compatible with the container closure system.

Reviewer Comment: The results of the functionality study met the criteria. The same vial adapter is used with the primary packaging components as used for Kogenate-FS and Kovaltry and have been used for many years. Issues regarding the use of the vial adapter would be noted in review of the complaints during a surveillance inspection and the recent inspections have not noted any such issues. No further review of the functionality is warranted for Jivi.

Primary Packaging Acceptance Activities
At receipt of the vials, Bayer performs a visual inspection in which defects are calculated according to respective AQL levels, dimensional analysis, and verifies the Certificate of Analysis from the vendor in which the prescribed (b) (4) tests requirements must be met.

Bayer provided the specifications that must be met by the stopper. Bayer performs a visual inspection to ensure compliance with AQL levels, dimensional analysis,(b) (4) testing (specification – maximum (b) (4) (specification – maximum (b) (4) stoppers), and a range of (b) (4) testing. In addition, the stoppers must meet the physical and chemical tests required by (b) (4)

Reviewer Comment: As noted previously, Bayer is using the (b) (4) vial, stopper, and aluminum seal that is approved for use with Kogenate-FS and Kovaltry. DMPQ does not have any review issues regarding the container closure of the vial/stopper combination which is used for Jivi.

FACILITY DESCRIPTION: BAYER HEALTHCARE LLC (b) (4)
Bayer produces the drug substance and the drug product of Kovaltry at their facility in (b) (4) The following summarizes the facility information for the manufacture of Kovaltry.

BUILDINGS USED IN MANUFACTURE OF KOVALTRY
The following summary describes each building that is used in the manufacture of Kovaltry at the Bayer (b) (4) campus the activities which are performed in the respective building.

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

Building (b) (4) Drug Substance

- (b) (4)

Building (b) (4) Warehouse, Packaging

- (b) (4)

Building (b) (4) Sterile Fill & Finish Facility (Drug Product)

- Pre-bulking, bulking, and sterile filtration
- Filling of sterile-filtered bulk into vials in aseptic processing area
- Freeze-drying of filled vials
- Capping

Buildings (b) (4))

- Analytical testing laboratories

Note: This list of buildings and building usage is the same as for Kovaltry.

Multi-Product Building Use

This section will describe the facility controls that are in-place for Buildings (b) (4) Drug Substance, Building (b) (4) Warehouse, Packaging, and Building (b) (4) Sterile Fill & Finish Facility (drug product) as these buildings are used to manufacture multiple recombinant DNA-derived therapeutic protein products and are denoted as multi-product facilities.

In Buildings (b) (4) Drug Substance and Building (b) (4) Sterile Fill & Finish Facility, the following products are manufactured:

- Kogenate-FS, Recombinant DNA-derived therapeutic protein, Licensed product
- Kovaltry, Recombinant DNA-derived therapeutic protein, Licensed product
- Jivi, PEGylated Recombinant DNA-derived therapeutic protein, Seeking licensure (subject of this BLA)

All three products are recombinant DNA-derived therapeutic proteins, originating from the (b) (4) baby hamster kidney cells. All three products are lyophilized and require reconstitution for intravenous injection.

BUILDING (b) (4) DRUG SUBSTANCE

The three products are manufactured on (b) (4) manufacturing schedules in Building (b) (4). Building (b) (4) The following table describes the activities for each product that are manufactured in the different plants.

Multi-product Usage of Suites of Building (b) (4) Drug Substance

(b) (4)

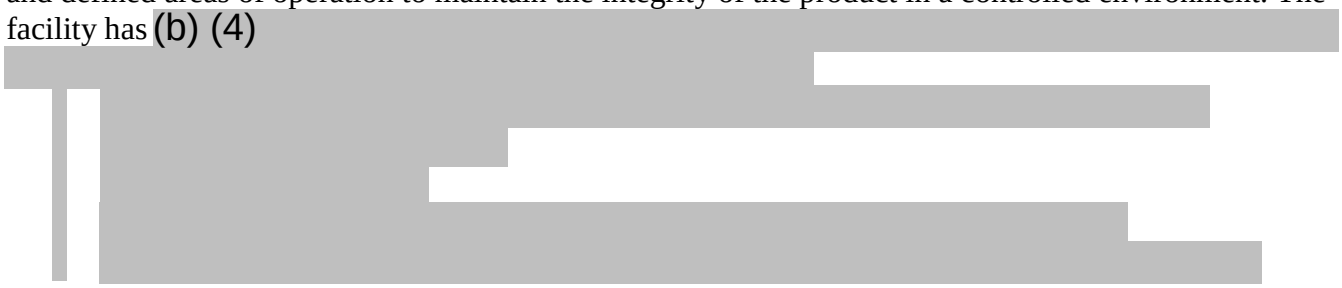
(b) (4) is dedicated to the manufacture of the licensed Kogenate-FS product while (b) (4) is intended for multi-product use as indicated in the table above

(b) (4)

Cleaning validation is performed for all shared product-contact equipment. The cleaning validation methodology for cleaning Kovaltry and Jivi from all the shared equipment was conducted concurrently during manufacturing utilizing the equipment soiled during production.

Contamination/Cross-Contamination Controls

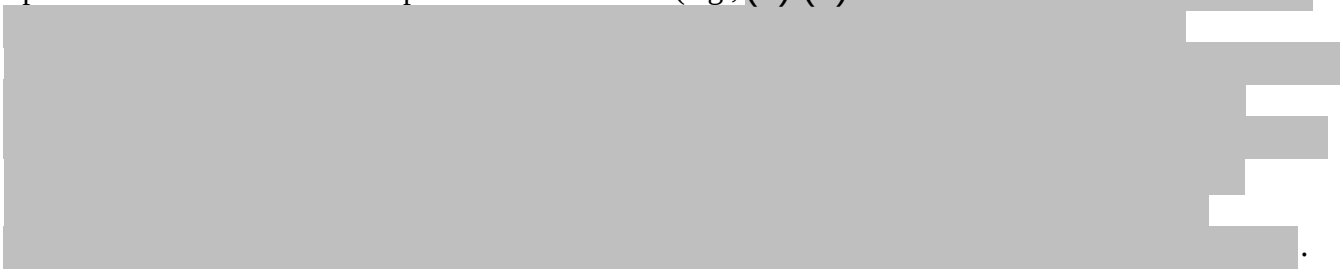
The multipurpose facility for the manufacture of drug substance has been designed to provide separate and defined areas of operation to maintain the integrity of the product in a controlled environment. The facility has (b) (4)



Reviewer Comment: The contamination and cross-contamination controls appear adequate to minimize the potential for contamination between the three products. The controls were evaluated during the recent ORA surveillance inspection in (b) (4) and do not warrant review for this BLA.

HVAC

The HVAC system in Building (b) (4) has several air handling units (AHU) which are dedicated to separate operational areas (e.g., media/solution preparation, cell culture, purification), and within an operational area to allow for separation of activities (e.g., (b) (4)



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Airlocks for passage of personnel, materials and equipment are located throughout the facility to maintain the integrity between areas of differing environmental standards.

Reviewer Comment: The HVAC system was reviewed during the recent ORA surveillance inspection and does not warrant additional review under this BLA as the same system and rooms are used for Kovaltry and Jivi.

Personnel, Material, Product, Equipment and Waste Flows

Limited access of personnel to production areas is controlled (b) (4) . Gowning procedures and personnel flow are established in order to minimize contamination of the product. Production personnel perform a (b) (4) gowning process before entry into a production area.

Site handling procedures are in-place to minimize contamination from incoming and outgoing material, product and equipment, and also for removal of waste. Segregation of lots to minimize cross-

contamination is provided by labeling of processing equipment, material and product containers with a specific lot number and by batch record control.

Materials and equipment are decontaminated per established procedure before entry into production areas and are additionally cleaned and sanitized using approved agents prior to entry into the classified areas. (b) (4) materials are restricted from entry into the classified areas. Product contact equipment is cleaned, sanitized or sterilized using validated cycles prior to use. Cleaning areas are also maintained within the same operational area for prevention of contamination between areas.

All raw materials are sanitized on entry according to documented procedures in airlocks or wipe down rooms prior to being transferred to a higher classification area.

Flow of (b) (4) is achieved by transferring from (b) (4) to the process areas using (b) (4). This provides a contained system between the preparation and operational areas with minimum exposure of materials to the environment.

Liquid waste is transferred to a (b) (4). Solid waste, including used (b) (4) exiting the production areas, to the waste disposal area.

In the BLA, Section 3.2.A.1 Facilities and Equipment, the following flow diagrams of Building (b) (4) were provided:

Reviewer Comment: DMPQ performed a review of the facility flow diagrams of Building (b) (4) as provided in the BLA; no review issues were noted. The flows were evaluated during the surveillance inspection as well without issue.

Area Cleaning and Monitoring
All areas are included in established cleaning schedules, with frequency and stringency based on the functions performed in the areas. Environmental monitoring is performed on a predetermined frequency to assure that the HVAC system and the cleaning procedures meet the classification requirements of the area.

Reviewer Comment: As the same drug substance facility is used for the manufacture of Kogenate-FS and Kovaltry, approved products, the establishment of the facility cleaning schedule and demonstration

of facility cleaning effectiveness is covered under the surveillance inspection for those products. No review issues are noted regarding facility cleaning.

Inventory Control

The drug substances are labeled with the product name and lot number at the time of manufacture, and stored in appropriate locations per storage condition requirements. Usage of raw materials, intermediates or drug substances is controlled by an inventory control system in combination with a predefined recipe. The drug substances are also tested for (b) (4) with analytical capability of distinguishing between the products.

BUILDING (b) (4) STERILE FILL & FINISH FACILITY (DRUG PRODUCT)

At the Bayer (b) (4) campus, Building (b) (4) is operated as a multi-product facility for the manufacture of the approved drug products, Kogenate-FS and Kovaltry, and for the proposed product, Jivi. Only (b) (4) is manufactured (b) (4) in each of the processing areas:

- (b) (4)

Contamination Control Measures

Line clearance and routine sanitization are performed (b) (4), regardless of product type. Line clearance includes verification that items from the previous product lot, such as vials, stoppers, caps, filling equipment, bulking equipment, are removed. Additional mitigations include:

- (b) (4)

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Procedural, physical and environmental practices are designed to prevent contamination. Contamination risk is mitigated through control of:

- Area Environment
- Personnel
- Workflow and Access Control
- Cleaning and Sanitization

Air handling units dedicated to separate operational areas (e.g., bulking, filling, freeze dryer loading and unloading) ensure separation of operations and maintain (b) (4). Airlocks for passage of personnel, materials and equipment maintain the integrity of areas of differing classifications.

Sterile product is exposed only to Class (b) (4) environment with Class (b) (4) background. The Class (b) (4) environments are delineated from the surrounding Class (b) (4) area by (b) (4)

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Area-specific gowning provides increasing levels of protection to the product. Personnel access into and out of the Class (b) (4) area is (b) (4) gowning and de-gowning operations. Materials and

equipment are cleaned, sanitized or sterilized per established validated procedures before entry into production areas.

Waste and items for cleaning exit from the Class (b) (4) area through a dedicated (b) (4) material pass-through. Waste items exit from the Class (b) (4) area to outside the facility through a dedicated (b) (4) material pass-through.

Validated cleaning/sanitization schedules are established for all areas. Environmental monitoring is performed on a predetermined frequency.

Reviewer Comment: As the same areas in Building (b) (4) are used for the drug product manufacture of Kogenate-FS, Kovaltry and Jivi, these areas have been inspected previously to assess the facility related control measures. The surveillance inspection performed of this area in (b) (4) did not reveal systemic concerns regarding the drug product facility. A review of the contamination control measures for the facility was performed under the review of Kovaltry BLA 125574/0 and found to be acceptable. The control measures appear adequate to prevent cross-contamination between the products produced in the building; therefore, further review of the information is not warranted.

HVAC

The HVAC system in Building (b) (4) has several air handling units which are dedicated to separate operational areas (e.g., bulking, filling, freeze dryer loading and unloading). The AHUs are sized and balanced to maintain (b) (4) is maintained.

Airlocks for passage of personnel, materials and equipment maintain the integrity of areas of differing classifications.

The Class (b) (4) environments are (b) (4) areas surrounded by a Class (b) (4) environment which is also (b) (4) . The Class (b) (4) environments are delineated from the surrounding Class (b) (4) area by (b) (4) All Grade (b) (4) rooms are supplied with air via (b) (4)

Reviewer Comment: As the same building and areas are used to produce the drug products for the licensed products, Kogenate-FS and Kovaltry, and the proposed product, Jivi, the qualification of the HVAC system in Building (b) (4) does not require review under this BLA as the HVAC system was recently reviewed during the ORA surveillance inspection in (b) (4)

Personnel Access and Gowning

Limited access of personnel to production areas is controlled (b) (4) . Area-specific gowning provides increasing levels of protection to the product. Personnel access into and out of the Class (b) (4) area is (b) (4) gowning and de-gowning operations.

Reviewer Comment: As the same areas in Building (b) (4) are used for the three products and these areas were reviewed during the ORA surveillance inspection in (b) (4), additional review of these topics are not warranted for this BLA.

Material, Product, Equipment and Waste Flows
The movement of all materials, components, equipment and waste into or out of the facility and between areas of different classification is controlled by pass-throughs and written procedures. Materials and equipment are cleaned, sanitized or sterilized in accordance with established validated procedures before entry into production areas and for re-use. For entry into the Class (b) (4) area, all product contact parts and components are (b) (4); all other components, parts, materials and equipment are (b) (4).

Waste and items for re-cleaning exit from the Class (b) (4) area through a dedicated (b) (4) material pass-through. Waste items exit from the Class (b) (4) area to outside the facility through a dedicated (b) (4) material pass-through. (b) (4) materials are prohibited from entry into the classified (b) (4) through (b) (4) areas.

In the BLA, Section 3.2.A.1 Facilities and Equipment, the following flow diagrams of Building (b) (4) were provided:

- (b) (4)

Reviewer Comment: DMPQ performed a review of the facility flow diagrams of Building (b) (4) as provided in the BLA; no review issues were noted.

Area Cleaning/Sanitization and Monitoring
Schedules for validated cleaning/sanitization are established for all areas. Environmental monitoring is performed on a predetermined frequency to assure that the HVAC system and the cleaning procedures meet the classification requirements of the area.

Reviewer Comment: As the same facility is used for the manufacture of the approved products (Kovaltry-FS, and Kovaltry), the establishment of the facility cleaning schedule and demonstration of facility cleaning effectiveness is covered under the ORA surveillance inspection (b) (4) No review issues are noted regarding facility cleaning.

Inventory Control
The drug products are labeled with the lot number at the time of manufacture, and stored in appropriate locations per storage condition requirements. Usage of raw materials, intermediates or drug substances is controlled by an inventory control system in combination with a predefined recipe. The drug substances are also tested for (b) (4) with analytical capability of distinguishing between the products.

Product Change-Over

Only one product is manufactured at a time in each of the processing areas:

a) (b) (4)

Line clearance of all product and components such as vials, stoppers, caps, filling equipment, bulking equipment is performed between processing of different production lots. Line clearance and routine sanitization of the line are performed between processing of production lots, regardless of product type.

Additional mitigations in place, which are relevant to product change-over are:

- (b) (4)

Reviewer Comment: The controls as described in this section which Bayer has in-place to control the drug product manufacturing activities in Building (b) (4) appear acceptable in which to minimize the potential for cross-contamination or mix-up between the drug products of Kogenate-FS, Kovaltry, and Jivi.

Utilities

Facility Water

Building (b) (4) generates their own Water for Injection (WFI) using purified water supplied from the (b) (4) . The generated WFI is supplied to the building storage and distribution system. WFI (b) (4) . Building (b) (4) generates the Water for Injection (WFI) using (b) (4) The WFI is (b) (4)

Bayer performs the following testing on the WFI: (b) (4) . For purified water, the same testing as WFI is performed (b) (4) .

In Building (b) (4) . Bayer performs (b) (4) .

Bayer states that the utility system for WFI and (b) (4) were qualified to ensure proper generation, distribution, and storage (if applicable).

Compressed Gases

For the drug substance manufacture in Building (b) (4) the compressed gases with product contact (b) (4) before distribution to production areas. The utility systems for compressed gases (b) (4) were qualified to ensure the proper generation, distribution, and storage of utilities (as appropriate).

Process air is tested for (b) (4) (based upon risk assessment and area qualification site monitoring study), (b) (4) .

The only compressed gas used in the drug product process is (b) (4) in the building. The (b) (4) at each point-of-use.

Waste

Liquid waste from production is (b) (4) .

Waste management systems were qualified for proper (b) (4)

Reviewer Comment: As the manufacture of Jivi is occurring in the same buildings as the approved products, Kogenate-FS and Kovaltry, the ORA inspection of the (b) (4) campus in (b) (4) included the use of the utility systems and the quality monitoring results of the water systems (WFI, purified water) and of the compressed gases. No additional review data is necessary regarding the water systems or compressed gases as this was covered during the ORA inspection for Kogenate-FS and Kovaltry.

HVAC

The heating, ventilating and air conditioning (HVAC) system qualification included IQ/OQ/PQ. The HVAC system was balanced and tested to ensure proper (b) (4) were maintained. The facility qualification demonstrated the facility is in a state of control and is fit for its intended use.

Facilities are continuously monitored by the (b) (4) and/or the (b) (4) for temperature and differential pressure. The pressure differentials are maintained positive relative to the surrounding areas of lower air cleanliness.

Reviewer Comment: As existing buildings are used for the manufacture of Jivi, the review of the HVAC qualification and building monitoring system are not warranted for this BLA as it has been previously reviewed during the review of Kovaltry and during surveillance inspections of the facility.

Environmental Monitoring

The production areas were qualified using environmental monitoring (EM) of surfaces, (b) (4)

Routine EM is performed to demonstrate conformance to established alert and action limits per standard operating procedures and are within (b) (4) requirements. Routine monitoring includes (b) (4) .

Routine EM of biosafety cabinets/unidirectional airflow hoods are monitored for (b) (4) . If a test result exceeds the action level, it is reported, documented, investigated and corrective actions are taken per standard operating procedures.

The number and location of samples for routine environmental monitoring are based on risk assessment, area qualification and post qualification site monitoring history. Site location considerations include area classification, intended use, physical characteristics, proximity to critical processes, components and open product, and equipment, product and personnel flow. Personnel working in aseptic processing areas are sampled for surfaces (glove and gown).

Building (b) (4) (drug substance) has Class (b) (4) environmental areas along with (b) (4) air flow hoods (monitored to Class (b) (4 requirements). Building (b) (4) (drug product) has Class (b) (4) areas along with (b) (4) air flow hoods (monitored to Class (b) (4 requirements). For areas classified as Class (b) (4) and the (b) (4) are monitored.

Reviewer Comment: The environmental monitoring that is occurring in Buildings (b) (4) has been established under the Kogenate-FS and Kovaltry manufacturing processes and the same monitoring frequency and monitoring types will be in use during the manufacture of Jivi. No review issues are noted in the review of the environmental monitoring plans for Jivi. Also, the environmental monitoring trend data are reviewed during surveillance inspections of the facility.

BUILDING (b) (4) PACKAGING AND WAREHOUSE FACILITY

Building (b) (4) is a multi-product packaging and warehouse facility which is used for Kogenate-FS, Kovaltry, and Jivi. The design of the facility and equipment, in conjunction with production scheduling, documentation, and equipment use procedures ensure that multiple products can be manufactured in the facility in accordance with current good manufacturing practices.

Reviewer Comment: As the same warehouse is used for Kogenate-FS and Kovaltry, the state of the warehouse facility was assessed during the surveillance inspection in (b) (4) therefore no additional review is warranted as part of the review for Jivi.

STERILE DILUENT ((b) (4)

The sterile water for injection (sWFI) diluent which is used for reconstitution of the Jivi drug product is manufactured by (b) (4) The diluent is supplied as a prefilled syringe in a 2.5 mL size. Bayer also uses (b) (4) to produce the sterile diluent for the currently licensed Kogenate-FS and Kovaltry products. The diluent sizes supplied with those products are 2.5 mL and 5.0mL.

The container for the 2.5 mL sWFI is a clear, colorless, borosilicate glass, (b) (4) 3 mL syringe. The nominal(b) (4) . The plunger stopper is a grey fluoropolymer-laminated, bromobutyl rubber. The tip-cap is a grey isoprene/bromobutyl rubber stopper. These are the same primary packaging components as the diluent supplied with Kovaltry (approved in BLA STN 125574/0).

The facility table identifies the (b) (4) locations where the 2.5mL diluent syringe is manufactured, release tested, and visually inspected. Note, the (b) (4) locations identified in the facility table are the

same (b) (4) locations used for the diluent supplied with Kovaltry. The 2.5mL diluent manufacturing process produces the same quality of diluent in the same syringe used by Bayer for all products (Kogenate-FS, Kovaltry, and Jivi). As identified in the facility table, all (b) (4) locations involved in the manufacture of the 2.5mL syringe or in quality release testing have all been recently inspected (i.e. within the last 2 years) and have good compliance histories (meaning no warning letters or official action indicated have been issued).

Noting the use of the same diluent manufacturer, (b) (4), with the diluent being supplied for Jivi in the same syringe size as for Kovaltry, a review of the process validation, equipment qualification, container closure integrity did not seem warranted for the diluent produced by (b) (4) as this was previously reviewed under the Kovaltry BLA (STN 125574/0). To confirm the information was the same or similar, I review the noted sections below. The summary below notes all pertinent similarities or differences compared to the information reviewed under the Kovaltry BLA.

3.2.P.1 Description and Composition of the Sterile Diluent – Pre-filled Syringe (2.5 mL)

- These sections describe the appearance of the finished product, clear liquid, and note the primary packaging materials for the syringe, plunger stopper, and tip cap stopper. The primary packaging materials of the diluent are the same as reviewed under the Kovaltry BLA. The primary packaging materials are included in the summary description of this section.

3.2.P.2 Pharmaceutical Development: Container Closure – System, Integrity Testing

- This section has two dossier sections on container closure. The first section provides further details on the primary packaging while the second section provides information on container closure integrity. The container closure method validation and the lot used in the integrity testing are the same as provided for review under the Kovaltry BLA. The results and method validation were reviewed under the Kovaltry BLA and do not require further review for this BLA as the manufacturing process for the diluent has not changed nor has the primary packaging.

3.2.P.3 Manufacture: Manufacturing Sites

- This section identifies the manufacturing sites where the diluent is manufactured and tested. This information has been reviewed and is included in the facility table of the memo. The (b) (4) sites did not require an inspection under this BLA due to their surveillance history; the rationale for waiving inspections of the facility sites is outlined in the Inspection Waiver for (b) (4).

3.2.P.3 Manufacture: Description of Manufacturing Process and Process Control

- The manufacturing process description for the manufacture of the diluent, 2.5mL size, was reviewed and compared to the process provided under the Kovaltry BLA. The process description along with in-process controls remain the same as previously reviewed. It is noteworthy to highlight than any process changes would be captured under the change control process at (b) (4) and reviewed during the surveillance inspections.

3.2.P.3 Manufacture: Control of Intermediates and Critical Steps

- The in-process control limits measured during the (b) (4) were provided and compared to the limits for the diluent produced for the Kovaltry BLA; no changes.

3.2.P.3 Manufacture: Process Validation (2.5mL pre-filled syringe)

- PV Summary 1: In this summary, the validation of the manufacturing process of the diluent 2.5mL syringes was performed. The validation summary was compared to the summary provided with the Kovaltry BLA and the summary is the exact same as the same validation batches were referenced.
- PV Summary 2: In this BLA, a second process validation summary was provided which contained summaries of the following process steps: (b) (4) Note, the results of the diluent process validation batches following (b) (4) were provided in the original process validation report. This validation report focuses on the (b) (4) process parameters and autoclave qualification/re-qualification. DMPQ reviewed this summary and key notes are provided.

  The summary explained that (b) (4) of the diluent is achieved through the (b) (4) method in which a (b) (4) is used for commercial production. A process validation was performed wit (b) (4) all syringes met this criteria from (b) (4) batches. During routine (b) (4)

  The summary also explained the requalification of the (b) (4) performs on an (b) (4) basis to ensure the (b) (4) is achieved. The (b) (4) were initially qualified and are subsequently requalified on an (b) (4) basis. Requalification is performed using a (b) (4) The summary report states that the validation of the (b) (4) was effective as there was (b) (4) in the initial validation studies and all requalification studies have resulted in (b) (4) as well.

  Overall, the report provides a summary of the (b) (4) method and routine re-qualification of the autoclave. DMPQ does not have any issues with the information provided. It is noted that (b) (4) is routinely inspected by ORA and as such the surveillance inspections will include a review of the manufacturing process including the routine requalification of the (b) (4) . Given the favorable outcomes of the recent inspections of the (b) (4) facilities, additional scrutiny of the process is not warranted.

3.2.P.5 Control of Drug Product (Release criteria and batch analyses)

- In this section, the release tests for the finished diluent along with the criteria are provided. The release tests and the criteria are the same as previously reviewed. It is noted one additional product test for (b) (4) has been added; however, this test is the responsibility of OTAT to assess. The (b) (4) and sterility tests and criteria remain the same as reviewed for the diluent under the Kovaltry BLA.

3.2.P.7 Container Closure System (Packaging material descriptions, specifications, test procedures)

- The information provided regarding the primary packaging materials, specifically the syringe, plunger stopper, and tip cap were compared to the information provided during the Kovaltry BLA review. The information is the same as the primary packaging materials have not changed for the 2.5mL diluent. No further review is necessary as this information was covered under Kovaltry BLA STN 125574/0.

Reviewer Comment: The information provided in this BLA for the sterile diluent manufactured and tested by (b) (4) is the nearly (b) (4) to the information provided in the Kovaltry BLA (albeit additional information on the (b) (4) noted in process validation summary #2). Based on the information summarized above and the outcomes of the recent surveillance inspections of the (b) (4) sites noted in the facility table of this memo, additional review of the sterile diluent for this BLA is not warranted.

STERILE DILUENT (BAYER (b) (4)

With this BLA, Bayer Healthcare LLC is seeking the approval of a second sWFI diluent manufacturer, Bayer (b) (4). The diluent will be used for reconstitution of the Jivi drug product as well. Like the diluent manufactured by (b) (4) the diluent manufactured by Bayer (b) (4) is supplied as a prefilled syringe in a 2.5 mL size. Bayer also uses Bayer (b) (4) to produce the sterile diluent in the 2.5mL size for the currently licensed Kovaltry product. Bayer Healthcare LLC submitted a PAS seeking approval for the use of Bayer (b) (4) as a second diluent supplier for the Kovaltry product under STN 125574/52. The PAS was approved by CBER on September 8, 2016. (Note, I was the DMPQ reviewer on this Supplement).

The container for the 2.5 mL sWFI is a clear, colorless, borosilicate glass, (b) (4), 5 mL syringe (max fill volume). The fill size target is 2.5mL with a (b) (4) . The plunger stopper is a grey fluoropolymer-laminated, bromobutyl rubber. The tip-cap is a grey bromobutyl rubber stopper. These are the same primary packaging components as the diluent supplied with Kovaltry and reviewed under PAS STN 125574/52.

The facility table identifies the Bayer (b) (4) facility where the 2.5mL diluent syringe is manufactured, release tested, and visually inspected. A pre-approval inspection for this facility location was waived due to the favorable compliance history of this location.

Noting the use of the same diluent manufacturer, Bayer (b) (4), with the diluent being supplied for Jivi in the same syringe size as for Kovaltry, a review of the process validation, equipment qualification, container closure integrity did not seem warranted for the diluent produced by Bayer (b) (4) as this was previously reviewed under the Kovaltry product supplement (PAS STN 125574/52). To confirm the information was the same or similar, I review the noted sections below as provided in this BLA. The summary below notes all pertinent similarities or differences compared to the information reviewed under the Kovaltry product PAS.

3.2.P.1 Description and Composition of the Sterile Diluent – Pre-filled Syringe (2.5 mL)

- These sections describe the appearance of the finished product, clear liquid, and note the primary packaging materials for the syringe, plunger stopper, and tip cap stopper. The primary packaging

materials of the diluent are the same as reviewed under the Kovaltry product PAS. The primary packaging materials are included in the summary description of this section.

3.2.P.2 Pharmaceutical Development: Container Closure System and Integrity Testing

- This section has two dossier sections on container closure. The first section provides further details on the primary packaging while the second section provides information on container closure integrity. The container closure method validation and the lots used in the (b) (4) testing are the same as provided for review under the Kovaltry product PAS. The results and method validation were reviewed under the Kovaltry product PAS and do not require further review for this BLA as the manufacturing process for the diluent has not changed nor has the primary packaging.

3.2.P.3 Manufacture: Manufacturing Sites

- This section identifies the manufacturing site where the diluent is manufactured and tested. This information has been reviewed and is included in the facility table of the memo. The Bayer (b) (4) site did not require an inspection under this BLA due to their surveillance history; the rationale for waiving the inspection of the facility site is outlined in the Inspection Waiver for Bayer (b) (4).

3.2.P.3 Manufacture: Description of Manufacturing Process and Process Control

- The manufacturing process description for the manufacture of the diluent, 2.5mL size, visual inspection, and packaging were reviewed and compared to the process provided under the Kovaltry product PAS. The process description for these steps remains the same the same as previously reviewed. The in-process controls and criteria remain the same. The process parameters and limits remain the same as well. It is noteworthy to highlight than any process changes would be captured under the change control process at Bayer (b) (4) and reviewed during the surveillance inspections.

3.2.P.3 Manufacture: Control of Intermediates and Critical Steps

- The in-process control limits measured during the (b) (4) were provided and compared to the limits provided for the diluent process under the Kovaltry product PAS; no changes were identified for the in-process control limits.

3.2.P.3 Manufacture: Process Validation (2.5mL pre-filled syringe)

- PV Summary 1: In this summary, the validation of the manufacturing process of the diluent 2.5mL syringes was performed which covered the bulking and filling process steps. The validation summary was compared to the summary provided with the Kovaltry product PAS and the summary is the exact same with the same validation batches being referenced. No further review of this summary report is necessary as it was reviewed in-depth under PAS STN 125574/52.

- PV Summary 2: In this summary, the validation of the (b) (4) process of the syringes was summarized. The validation summary was compared to the summary provided with the Kovaltry product PAS and the summary is the exact same with the same validation batches being referenced and the same autoclave. No further review of this summary report is necessary as it was reviewed in-depth under PAS STN 125574/52.

3.2.P.5 Control of Drug Product (Release criteria and batch analyses)

- In this section, the release tests for the finished diluent along with the criteria are provided. The release tests and the criteria are the same as previously reviewed. The sterility criteria is "sterile" (no viable microorganisms detectable). The (b) (4) criteria is (b) (4). These tests and criteria have not changed.

3.2.P.7 Container Closure System (Packaging material descriptions, specifications, test procedures)

- The information provided regarding the primary packaging materials, specifically the syringe, plunger stopper, and tip cap were compared to the information provided during the Kovaltry product PAS review. The information is the same as the primary packaging materials have not changed for the 2.5mL diluent. No further review is necessary as this information was covered under Kovaltry product PAS STN 125574/52.

Reviewer Comment: The information provided in this BLA for the sterile diluent manufactured and tested by Bayer (b) (4) is identical to the information provided in the Kovaltry product PAS STN 125574/52 which was previously reviewed and approved. Based on the information summarized above and the outcomes of the recent surveillance inspections of the Bayer (b) (4) site noted in the facility table of this memo, additional review of the sterile diluent produced by Bayer (b) (4) for this BLA is not warranted.

FINAL LABELING & PACKAGING

In the BLA, specifically the Facilities and Equipment section and the Qualification/Validation of Facilities and Equipment section, details regarding the labeling of the Jivi drug product vials along with the packaging and labeling process of the contents of the Jivi market packages were not provided. The information was sparse and did not provide a detailed explanation of the labeling and packaging processes nor of the equipment used in these operations. Further details from Bayer was requested regarding these topics; note the following four information request items below.

Information Request #3, Question #6: Please provide detailed information on your packaging and labeling process for the Jivi drug product vials. In your response please include information such as the building location and packaging areas, labeling equipment including summary of qualification, and labeling control process. Please note if the packaging and labeling process for Jivi is the same or similar to the process for Kogenate-FS and/or Kovaltry. The information regarding the packaging and labeling process was not provided in sufficient detail to understand the process.

Bayer Response (Amendment #36): The packaging and labeling process occurs in (b) (4) building (b) (4) for Jivi (Damoctocog Alfa Pegol) and is the (b) (4) as for Kogenate-FS and Kovaltry. The packaging and labeling process qualification brackets all three products; test results and acceptance criteria are presented in Qualification/Validation of Packaging Equipment (Report summary #017012852-01).

Reviewer Comment: Bayer confirmed that the packaging and labeling process is the exact same for all three rFVIII products and as such, the process validation covers all three products. As the process is the same and has been previously reviewed under the Kovaltry BLA and covered during routing surveillance inspections; no further review of the labeling and packaging process is warranted for Jivi considering the packaging contents are nearly identical (except for labeling and package insert differences) to those contained in the Kogenate-FS and Kovaltry market packages.

Information Request #3, Question #7: Please explain the manufacturer who is responsible for performing the labeling of the sterile diluent pre-filled syringes. If Bayer Healthcare LLC (b) (4) site) is not responsible for this activity, please explain the incoming verification or testing that is performed on the sterile diluent pre-filled syringes.

Bayer Response (Amendment #36): The sterile diluent pre-filled syringes manufactured by Bayer (b) (4) and by (b) (4) are labeled at Bayer (b) (4) facility. Upon receiving at Bayer Healthcare LLC (b) (4) the labeled pre-filled syringes are tested and visually inspected against the product specifications, prior to the release to final packaging.

Reviewer Comment: Bayer (b) (4) performs the same functions for the sterile diluent supplied with Kovaltry. Following labeling at Bayer (b) (4), the sterile diluent is shipped to Bayer Healthcare LLC who performs incoming inspection on the diluents before releasing for final packaging; the process is the exact same for both Kovaltry and Jivi. No further review of the labeling of the diluent or incoming inspection at Bayer Healthcare LLC is warranted under this BLA.

Information Request #3, Question #8: Please provide information regarding the packaging and labeling of the market packages which contain the Jivi drug product, sterile diluents and reconstitution device(s).

Bayer Response (Amendment #36): The packaging and labeling process for Jivi (Damoctocog Alfa Pegol) is the same process as for Kogenate-FS and Kovaltry and is described in the Manufacturing Process – Packaging Process (Amendment BLA section P.3.3.4)

Reviewer Comment: Bayer confirmed that the packaging and labeling process is the exact same for all three rFVIII products and as such, the process validation covers all three products. As the process is the same and has been previously reviewed under the Kovaltry BLA and covered during routing surveillance inspections; no further review of the labeling and packaging process is warranted for Jivi considering the packaging contents are nearly identical (except for labeling and package insert differences) to those contained in the Kogenate-FS and Kovaltry market packages.

Information Request #3, Question #9: Please provide a summary of the final release activities that you perform to authorize the release for distribution of the final drug product package. Please ensure you include the criteria that must be met before distribution is authorized for Jivi.

Bayer Response (Amendment #36): A release for distribution is performed after the review of all associated batch records, facility/utility and microbiological assessments, test results/release specifications, deviations, changes, ambient tracking and expiration dating. The reviewed data must meet the established acceptance criteria as required in standard operating procedures. Any deviations generated in association with the processing of the batch, must be closed with a disposition to accept the batch for release.

Reviewer Response: The process for batch release appears acceptable and is consistent with industry practices. No issues are noted.

MEDICAL DEVICES

As part of the final market packages for Jivi, the following medical devices are included:

- Sterile diluent in a pre-filled syringe (considered a device)
- Vial adapter (b) (4))
- Administration set/Venipuncture set (b) (4)
- Administration set/Venipuncture set (Winged infusion set)(b) (4)
- Administration set/Venipuncture set (Winged infusion set with filter) (b) (4)

Additional information regarding the sterile diluent pre-filled syringe is covered in review memo sections "Sterile Diluent: (b) (4) " and "Sterile Diluent: Bayer (b) (4). Regarding the review of the medical devices, OTAT is responsible to review the drug delivery of the product with the vial adapter and administration sets. DMPQ is responsible to ensure Bayer is meeting the requirements of the 820 Quality Systems regulations applicable to co-packaged devices.

Vial Adapter

The vial adapter is a fluid transfer device that allows transfer of fluids between the diluent syringe and drug product vial as well as to the administration set. The rubber stopper is punctured by the integral plastic spike in the adapter. The vial adapter is manufactured by (b) (4) and is 510(k) cleared (b) (4) The same vial adapter part number, (b) (4), is used with Kovaltry.

As the same vial adapter will be used with Jivi with the same intended use and in the same patient population, the FDA agreed in a pre-BLA meeting that a human factors study would not be required for the Jivi product.

Reviewer Comment: In the review of the Kovaltry BLA, a consult from CDRH was included in the review committee and the CDRH reviewer performed a review of the vial adapter to ensure Bayer was meeting the requirements of the 820 regulations including performing incoming testing and purchasing controls for the vial adapter. As Bayer is using the same vial adapter as previously reviewed, a review of the purchasing controls and incoming acceptance testing is not warranted under this BLA. In addition, the vial adapter is cleared medical device.

Administration Sets

There are three administration sets for the drug delivery.

Administration set, (b) (4), is manufactured by (b) (4) . and is 510(k) cleared (b) (4) . This set is comprised of a polyvinyl chloride (PVC) tube equipped with a stainless steel cannula, Luer adapter, integral filter (b) (4)), and wings. A drawing of the device was provided in the BLA. **Note**, This set is used for the administration of Kogenate-FS and Kovaltry. The device review was completed by CDRH for Kovaltry which included review of the incoming material testing and purchasing controls. Further review related to Bayer's control over the device is not warranted for this BLA.

Administration sets (b) (4) are manufactured by (b) (4) 510(k) cleared (b) (4)). The 510k clearance includes both sets. The only difference between the two sets is set (b) (4) does not have a filter whereas set (b) (4) is supplied with a filter ((b) (4) Drawings of the devices were provided in the BLA.

Note, Set (b) (4) is supplied with Kovaltry. This set was included in the review by CDRH regarding Bayer's compliance with the device regulations. In Amendment #2 (OTAT CMC reviewer request), Bayer explained that administration sets (b) (4) are currently approved for administration of Kogenate-FS (STN 103332/6338). Bayer intends to (b) (4) .

Reviewer Comment: In the review of the Kovaltry BLA, CDRH assessed Bayer's quality systems regarding the acquisition and testing (i.e. purchasing controls) of the device components (vial adapter, administration sets) and found the quality systems were acceptable. Since the devices used for Jivi are the same devices used for Kogenate-FS or Kovaltry, a review of Bayer's quality systems applicable to the co-packaged device components is not warranted for this BLA as it has been reviewed previously and found to be acceptable.

SHIPPING STUDIES

Bayer has provided two shipping studies in this BLA, one shipping study for the drug substance and a second study for the shipping of the drug product. Each study was reviewed by DMPQ and summarized below for the respective product type.

SHIPPING OF THE DRUG SUBSTANCE

(b) (4)

(b) (4)

(b) (4)

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SHIPPING OF THE DRUG PRODUCT

The Jivi drug product is transported using temperature controlled shipping systems designed to maintain product integrity and control temperature. The shipping systems include (b) (4) that are qualified and/or continuously monitored to ensure temperature control during transport.

(b) (4) contain an (b) (4) temperature control system. When product is transported by any method other than a (b) (4), a (b) (4) shipping system is used. (b) (4) (b) (4) are both used for this purpose. (b) (4)

Unlabeled drug product (UDP) vials are individual glass vials with aluminum seal caps that are printed with the product batch number. The UDP vials are placed into (b) (4) for domestic shipment. Shipments of UDP vials to international destinations are carried out in Bayer-qualified shipping systems. The vials and/or cases must meet the incoming container and/or vial inspection procedural requirements at the destination site.

A market package consists of an individual labeled product vial, a diluent pre-filled syringe and other components necessary for patient administration within a carton. Multiple market packages are placed

into shipping cases. Shipping cases are stacked onto pallets and placed in (b) (4) for shipments.

Shipping studies, including (b) (4) testing, were performed on UDP vials and market packages in order to establish the suitability of the shipping processes. The purpose of the (b) (4) testing was to ensure that packaging design adequately protects product from damage during shipment. The purpose of the (b) (4) testing was to ensure that the temperature control system maintains product temperature within an acceptable range throughout transport. The shipping studies utilize approved rFVIII commercial products and shipping system components and configurations.

Physical Testing
Physical testing involved exposing the shipping configurations to (b) (4)

For the UDP shipping test, the test configuration included (b) (4) The results met the criteria indicating the packaging for the market packages is satisfactory to prevent damage to the individual components.

Device Functionality Testing
Following distribution simulation per (b) (4) device functionality testing was performed on a sample size of (b) (4) market packages under worst-case shipping configurations to ensure the market package components properly functioned with the product vial for drug reconstitution and delivery as intended. Various quantities of market packages within (b) (4) were utilized to represent a range of masses and payload configurations, from minimum to maximum, including worst case conditions.

The criteria for the functionality test required the infusion set and vial adapter must function as intended as described in the package insert/instructions for use and no failures are permitted. The results of the (b) (4) market packages noted that all components functioned as intended following the simulation test per (b) (4) therefore, the packaging met the criteria.

Reviewer Comment: Bayer notes that only the market packages packed into the (b) (4) were functionally tested following the shipping simulation; there is no indication the market packages were functionally tested following packaging in the (b) (4) shipping configuration. Bayer is requested to explain this test omission.

Information Request #3, Question #4: Regarding your device functionality testing for the market packages, you have provided the results of the functionality testing of the market packages when packaged into the (b) (4) shipment configuration; however, you have not provided functionality testing of the market packages following transport simulation in the (b) (4) shipper configuration. Please

explain if the functionality testing for the market packages in the active (b) (4) was collected and if so, please provide a summary of the results. If not collected, please explain your rationale.

Bayer Response (Amendment #36): The device functionality test results for the market packages (MPs) in the (b) (4) are applicable to market packages shipped within (b) (4) . The (b) (4) are considered to be the worst case shipping system due to the nature of their distribution environment and exposure to potential hazards (elevated drop heights, carrier handling, exposure to extreme temperatures, etc.).

Reviewer Comment: Bayer is stating that the market package configuration in the (b) (4) are worst-case shipping configuration over the (b) (4) ; therefore, only the market packages contained within the (b) (4) were device tested. The justification for functionality testing of the market packages (worst-case shipment configuration) in the (b) (4) shipment configuration appears acceptable.

Thermal Testing
Thermal testing was performed to qualify the individual shipping systems ((b) (4) , separate from the physical testing. Shipping systems were successfully qualified by monitoring (b) (4)

(b) (4)

Acceptance criteria for the thermal testing were set based on the acceptable ranges established by drug product stability studies.(b) (4)

The results indicate that all systems passed the thermal requirement and no failures.

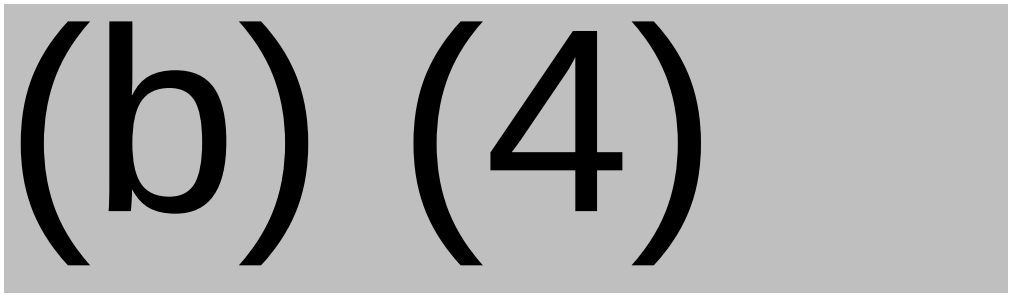
Bayer concludes that the qualification of temperature control systems along with continuous temperature monitoring where applicable, ensures that the shipping process for Damoctocog Alfa Pegol maintains adequate temperature control.

Reviewer Comment: Bayer has not provided sufficient information to understand the (b) (4) testing and payload size. The results indicate that (b) (4) payload was tested which contained various sizes of market packages. Bayer needs to provide justification that the shipper can maintain temperature during the transport regardless of the min or max size of the payload.

Information Request #3, Question #5: Regarding the (b) (4) thermal testing of the market packages as referenced from the Shipping Transport Study section and results table 3-5, there is insufficient information to understand the nature of the study to demonstrate the ability of the shipment to maintain transport temperature. Please address the following items:

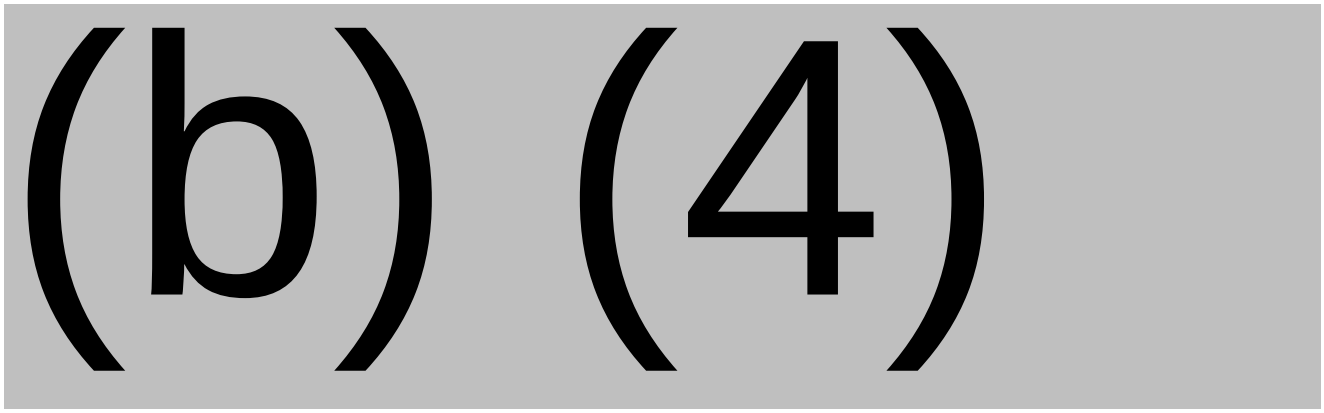
a. Please provide the shipment temperature range that must be maintained during the shipment of the market packages.

   Bayer Response (Amendment #36): A table was provided that shows the shipment temperature range that must be maintained during shipment of the market packages:



b. Please provide information on the payload sizes that were tested. The results table, Table 3-5, indicates 'various sizes' were tested however there is no description if these sizes were minimum or maximum loadings.

   Bayer Response (Amendment #36): The following two tables were provided for the payload sizes tested for the market packages shipped within (b) (4) and shipped within (b) (4).



(b) (4)

c. Please provide information on the shipper and the ability of the shipper to maintain the desired temperature range.

Bayer Response (Amendment #36): (b) (4) are utilized to ship Jivi (Damoctocog Alfa Pegol) market package orders from Bayer (b) (4) to domestic continental USA customer destinations via (b) (4). A market package (MP) consists of an individual labeled product vial, a diluent prefilled syringe and other components necessary for patient administration within a carton.

(b) (4)

The ability of the shipping systems to maintain the desired temperature range is documented in response to Question #5b above.

d. Please explain if the (b) (4) was tested during the cold and hot seasons (worst-case temperature loads).

Bayer Response (Amendment #36): (b) (4)

Question #5a above, the simulated thermal testing sufficiently challenged the shippers to hot and cold conditions.

(b) (4)

Reviewer Comment: In the response to Question #5c, Bayer notes that the market packages are shipped from the Bayer facilities in (b) (4) to the end-user (i.e. customer). The information regarding the (b) (4) is new to the BLA and has not been described elsewhere. It is unclear if this is a second distribution site; follow-up with Bayer regarding this site is needed for clarification. Second, the shipping purview covers the shipment of the final drug product from the packaging/labeling facility to the distributor. Once the drug product leaves the distributor, the shipping is not under the purview of DMPQ and is considered outside the license. Therefore, since Bayer has provided the information related to the thermal and functional testing of the market packages following shipment from the distribution center, the information does not require review. This information was not clear in the BLA. The following IR will be sent to regarding the distribution location(s) for the finished drug product.

Information Request #4, Question #1: In your response dated May 4, 2018 to Question #5c, you identify that market package orders can be shipped from (b) (4) facilities to domestic customers. Information regarding distribution is not clear in the BLA or the May 4, 2018 amendment; therefore, please address the following:

a. Please clarify the distribution location(s) for the finished market packages of Jivi (i.e. the finished package which contains the Jivi drug product, diluent, and administration devices). In your response, please clearly list the company name and address. Please explain if these site(s) are responsible to ship the market package to the end-user or customer.
b. Information regarding the (b) (4) facility was not provided in the BLA or in the 356h form submitted with the BLA. Please identify the responsibilities of this site as it pertains to the Jivi product.

Bayer Response (Amendment #42): (A& B combined) The finished market packages of Jivi are distributed to US customers such as CVS, pharmacies, and hospitals by Bayer Healthcare LLC at the following locations:

- (b) (4)

Bayer apologies for the inadvertent omission of the (b) (4) site from the BLA and 356h form. A revised 356h form has been provided in this amendment. The responsibilities for this site for the Jivi product are warehousing and distribution.

Reviewer Comment: Bayer has identified a second distribution site for their market packages of Jivi, which is Bayer Healthcare LLC's facility in (b) (4). The revised 356h form appears acceptable and includes the pertinent information related to this site including the address, FEI #, and responsibilities of site. However, it is not clear if Bayer has executed a shipping validation of the market packages between the sites in (b) (4). Bayer has done shipping studies of the market packages

including functionality testing and physical testing though it is not understood if these studies cover the shipping conditions or if the information provided describes the shipping configuration (b) (4) and the shipping temperature requirements for the market packages. Therefore, additional information is needed regarding the shipment of the market packages to the (b) (4) site for distribution.

Information Request #5, Question #4: In the response dated May 25, 2018, you identified a second distribution site for the finished market packages of Jivi, specifically, Bayer Healthcare LLC located in (b) (4). Given the information about this second distribution site, please address the following questions and requests for information pertaining to the shipping of the finished Jivi market packages from your site in (b) (4). Please note, the information you have provided in the BLA (Section 3.2.A) and in the response dated May 4, 2018 appears to explain the shipping conditions of the market packages going from a distribution location to the customer/end-user; however, the shipping information does not appear to pertain to the shipment between your manufacturing site in (b) (4) and the second distribution site in (b) (4) therefore, this information is needed in order to continue the review of the BLA.

a. Please describe the shipping configuration (i.e. number of market packages in a box or container), type of shipping container used for transport (i.e. shipping system), along with the shipping environment and conditions.

   Bayer Response (Amendment #48): The Jivi market packages (MPs) are shipped from (b) (4), which contain an active temperature control system designed to monitor and control a 2 – 8°C environment. The MPs are placed within (b) (4). The dimensions of a sales case and MP and the load configuration are shown in Figure 4-1 provided in the response. The maximum quantity of MPs in a sales case is (b) (4).

b. Please describe how you ensure the shipping temperature is maintained during transit of the market packages. Please provide a summary of the studies you have performed to ensure the transit conditions are maintained and indicate if the studies include winter and summer seasons.

   Bayer Response (Amendment #48): To ensure the required shipping temperature is maintained for the shipment of MPs from (b) (4), the temperature of the palletized MPs within the (b) (4) is monitored and recorded for the duration of the shipment by temperature monitoring devices. The recorded temperature data is reviewed for product acceptance upon arrival at (b) (4).

   Thermal testing for (b) (4) distribution to the (b) (4) distribution center used (b) (4) was provided in document Description of Drug Product Shipping (Transportation) Studies and submitted in our response date May 4, as presented below in Table 4-1.

Table 4-1 from Response: Thermal Test Results for (b) (4) of Market Packages in (b) (4)

(b) (4)

c. Please describe the incoming acceptance activities that are performed at the (b) (4) site once the market packages are received from the (b) (4) site.

Bayer Response (Amendment #48): Upon arrival at (b) (4) is reviewed for confirmation of material number, batch number and quantity ordered/received. The temperature data collected by the temperature recording devices is reviewed for product acceptance and dispositioned accordingly.

d. Please explain if you have performed functionality testing of the market packages following the transit conditions to (b) (4) to ensure the final product continues to meet specifications following transit. If you are leveraging data from existing studies performed with the market packages, please indicate how these studies apply to cover the transit conditions and duration from (b) (4)

Bayer Response (Amendment #48): Please note that MPs destined to US customers from either (b) (4) . As described in document Description of Drug Product Shipping (Transportation) Studies, the device functionality testing was performed on MPs that were packed in (b) (4) following distribution simulation per standardized (b) (4) . This testing supports device functionality for MPs shipped within (b) (4) from (b) (4) (b) (4) distribution center because (b) (4) are considered to be the worst-case shipping system due to the nature of their distribution environment and exposure to potential hazards (elevated drop heights, carrier handling, exposure to extreme temperatures, etc.).

e. Please explain if you have performed transit (b) (4) testing for your finished market packages in which the (b) (4) testing covers the shipping conditions and duration between your sites in (b) (4) . Typically, such testing is performed in accordance with (b) (4) . If you are leveraging existing data, please explain how the data is applicable between your two sites as noted.

Bayer Response (Amendment #48): As described in document Description of Drug Product Shipping (Transportation) Studies, the physical transit (b) (4) testing was performed per standardized (b) (4) series test and included (b) (4) (b) (4) . The MP physical testing was performed (b) (4) , which also supports device functionality testing for MPs shipped in (b) (4) from (b) (4)

(b) (4)

Reviewer Comment: Overall, the information provided by Bayer in the BLA and in the multiple amendments provides assurance that temperature monitoring of the transit configurations are performed to ensure the temperatures during transit are within spec. Bayer has also performed transit (b) (4) testing per (b) (4) to demonstrate the market packages are functional following simulated transit (b) (4). The testing performed in similar to the testing performed for Kovaltry as well. Given the information provided, no further issues are noted regarding the shipment of the finished drug product in the final market package configuration.

ENVIRONMENTAL ASSESSMENT

Bayer provided a Categorical Exclusion Request for preparation of an Environmental Assessment in Section 1.12.14 of the BLA. Bayer is seeking the exclusion based upon 21 CFR Part 25 (31) which notes that biological products are exempted from the requirement of an environmental assessment. Bayer explains that Jivi is a recombinant B-domain deleted human coagulation Factor VIII variant which is site specifically conjugated with a branched polyethylenglycol (PEG). BAY 94-9027 is a replacement protein of the naturally occurring coagulation factor, Factor VIII. It is catabolized during human metabolism and no active molecule is excreted by the patient.

Reviewer Comment: There are two issues with the categorical exclusion that require clarification from Bayer, specifically:

1. The CE request is submitted by Bayer (b) (4) and not Bayer Healthcare LLC. Bayer Healthcare LLC is the BLA applicant and as such, should be making the CE claim. Bayer (b) (4) does not have a part in the manufacture of the drug substance or drug product.
2. Bayer has not identified which section of 21 CFR Part 25.31 they are seeking the exclusion; the regulation lists 10 different sections.

To address these issues, the following two IRs were sent to Bayer.

Information Request #1, Question #11: We acknowledge that the Categorical Exclusion Request for preparation of an Environmental Assessment as provided in BLA section 1.12.14 was prepared and signed by Bayer (b) (4) which is not the applicant of the BLA. Please submit a new Categorical Exclusion Request for preparation of an Environmental Assessment prepared and signed by the BLA applicant, Bayer Healthcare LLC. Also, please note the next request in preparation of your new Categorical Exclusion Request.

Information Request #1, Question #12: Regarding your Categorical Exclusion Request for preparation of an Environmental Assessment, you are seeking the request in accordance with 21 CFR Part 25.31. However, your request does not specify which specific section of 21 CFR Part 25.31 you are seeking the exclusion, please note the CFR lists 10 sections under Part 25.31. Please identify which specific section of 21 CFR Part 25.31 you are seeking the categorical exclusion request and the rationale.

Reviewer Comment: In Amendment #26, Bayer Healthcare LLC submitted a new categorical exclusion request under 21 CFR Part 25.31 (a). In the CE request, Bayer explains that Jivi is a recombinant B-domain depleted human coagulation Factor VIII variant which is site specifically conjugated with a branched polyethylenglycol (PEG). Jivi is a replacement protein of the naturally occurring coagulation factor, Factor VIII. It is catabolized during human metabolism and no active molecule is excreted by the patient.

Reviewer Comment: Concur with the request for the Categorical Exclusion under 21 CFR 25.31 (a) as Bayer has explained that Jivi has a recombinant replacement protein of the naturally occurring coagulation factor, Factor VIII, and that the protein is catabolized during human metabolism so that it is not excreted by the patient. By the protein being catabolized by the human user, the action does not increase the use of the active moiety.

Note, in review of the updated CE language, it was noted that Bayer did not provide language specific to 25.15(d) stating that "to the applicant's knowledge, no extraordinary circumstances exist". Bayer was contacted via IR#6 to provide the applicable language per CFR 25.15(d).

Information Request #6, Question #1: As required for a categorical exclusion claim per 21 CFR Part 25.15(d), you need to cite the particular categorical exclusion that is claimed (you are electing to claim the exclusion under 21 CFR part 25.31(a)), and state that to the applicant's knowledge, no extraordinary circumstances exist. In your categorical exclusion request provided in your response dated March 23, 2018, you have not included the specific language that "to the applicant's knowledge, no extraordinary circumstances exist" per 25.15(d). Please submit an amended categorical exclusion containing the specific statement listed above to demonstrate that you are indeed meeting the full requirements of 21 CFR Part 25.15(d).

Bayer Response (Amendment #49): A revised CE memo was provided specifically stating the following, "Per 21 CFR Part 25.215(d), and in accordance to 21 CFR part 25.31(a), Bayer Healthcare LLC is requesting a categorical exclusion from the environmental assessment requirement for the compound BAY 94-9027 (Antihemophilic Factor (Recombinant), PEGylated). Per 21 CFR Part 25.15(d), to the knowledge of Bayer Healthcare LLC, no extraordinary circumstances exist."

Reviewer Comment: The information provided by Bayer is acceptable to comply with 21 CFR 25.15(d) as outlined in the request.