



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
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Silver Spring, MD 20993-0002

To: Administrative File: STN 125574/0

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Applicant: Bayer Healthcare LLC

Product: Antihemophilic Factor (Recombinant), Trade name: Kovaltry

Intended Use: Treatment of Hemophilia A

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

Due Date: March 16, 2016

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) (trade name granted: Kovaltry), to be used in the treatment of Hemophilia A. Bayer currently holds license number 0008 for an antihemophilic factor product, Kogenate, which has been approved since 1993. The products of Kogenate/Kogenate-FS and Kovaltry are similar and have the same active ingredient; however, for the manufacture of Kovaltry, Bayer has implemented improvements in the drug substance manufacturing process. As with Kogenate-FS, the drug substance and drug product of Kovaltry will be manufactured by Bayer at their facility in (b) (4). As with Kogenate-FS, the Kovaltry drug product requires reconstitution with sterile water for injection diluent. The diluent is manufactured by (b) (4) and is supplied as a pre-filled syringe. As the delivery of Kovaltry requires medical device components in the administration set and the sterile diluent is provided as a pre-filled syringe, CRDH was requested as a consult for these aspects of the BLA. The submission was appropriately filed as a BLA according to 21 CFR 601.12a.

The supplement was submitted via the eCTD format and was received by CBER on December 16, 2014. The following sections were provided in the BLA; the responsible office (DMPQ, OBRR, or CDRH) is denoted for each section:

Module 1: Regional [DMPQ/OBRR]

1.1 FDA Forms 365h and 3397

1.2 Cover Letter

- Cover Letter [All]
- Reviewer's Guide [All]
- FDA Form 3674 – Clinical Trial Compliance [OBRR]

1.3 Administrative Information [OBRR]

- Debarment Certification
- Financial Certification and Disclosure (FDA Form 3454 and FDA Form 3455)

1.4 References

- Letters of Authorization (6) for Drug Master Files and 510(K) [OBRR/DMPQ]
- Cross-Reference to Previously Submitted Information (for Kogenate-FS)

1.6 Regulatory Meetings and Response Summaries [DMPQ/OBRR]

1.12 Other Correspondence

- Application for Product Name, Trademark naming rights [OBRR]
- Environmental Analysis – Categorical Exclusion [DMPQ]

1.14 Labeling [OBRR]

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

2.2 Introduction

2.3 Quality Overall Summary

- Introduction
- Drug Substance (Bayer) [OBRR/DMPQ]
- Drug Product – Lyophilized Product (Bayer) [OBRR/DMPQ]
- Drug Product – Sterile Diluent (b) (4) [OBRR/DMPQ]
- Drug Product – Facility and Equipment Info [DMPQ], Adventitious Agents [OBRR]
- Diluent - Facility and Equipment Info [DMPQ], Adventitious Agents [OBRR]
- Substrate Assay for Release of Drug Product [OBRR]

2.4 Nonclinical Overview [OBRR]

- Pharmacology, Pharmacokinetics, Toxicology

2.5 Clinical Overview [OBRR]

2.6 Nonclinical Written and Tabulated Summaries [OBRR]

2.7 Clinical Summary [OBRR]

Module 3: Quality

3.2.S Drug Substance (Bayer)

3.2.S.1 General Information [OBRR]

- Nomenclature, Structure, General Properties

3.2.S.2 Manufacture

- Manufacturing Sites [DMPQ]
- Manufacturing Process Flow Diagrams [OBRR/DMPQ]

- Raw Material Specifications & Testing [OBRR]
 - Validation of Intermediate Test Methods, Control of Intermediates [OBRR]; (b) (4) [DMPQ]
 - Process Validation [OBRR/DMPQ]
 - Process Validation Summary
 - Process validation – (b) (4)
 - Process Validation – (b) (4)
 - Process Validation – (b) (4)
 - Manufacturing Process Development [OBRR]
- 3.2.S.3 Characterization [OBRR]
- 3.2.S.4 Control of Drug Substance
- Specification [OBRR]
 - Analytical Test Procedures [OBRR] ((b) (4) – DMPQ)
 - Validation of Analytical Procedures [OBRR] ((b) (4) – DMPQ)
 - Batch Analyses [OBRR/DMPQ]
 - Justification of Specification [OBRR]
- 3.2.S.5 Reference Standards or Materials [OBRR]
- 3.2.S.6 Container Closure System [DMPQ/OBRR]
- 3.2.S.7 Stability [OBRR]
- 3.2.P Drug Product (Lyophilized Product – Bayer)
- 3.2.P.1 Description and Composition of the Drug Product [DMPQ/OBRR]
- 3.2.P.2 Pharmaceutical Development [OBRR/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 [OBRR]
 - Description of Manufacturing Process and Process Control [OBRR/DMPQ]
 - Control of Intermediates and Critical Steps (Bulk/Filling, Freeze Drying, Inspection/Warehouse) [OBRR]
 - Process Validation [OBRR/DMPQ]
 - Process Validation Summary
 - Process Validation – Bulk/Filling
 - Process Validation – Freeze Drying
- 3.2.P.4 Control of Excipient [OBRR]
- 3.2.P.5 Control of Drug Product
- Release and Shelf Life Specifications [OBRR]
 - Analytical Test Procedures [DBSQC]
 - Validation of Analytical Procedures [DBSQC]
 - Batch Analyses [OBRR/DMPQ]
 - Characterization of Impurities [OBRR]

- Justification of Specification [OBRR]
- 3.2.P.6 Reference Standards or Materials [OBRR]
- 3.2.P.7 Container Closure System
 - Description of Packaging Materials – Reconstitution cap, seal, vial, stopper [DMPQ/CDRH]
 - Specification and Test procedure – vial, cap, stopper [DMPQ/CDRH]
 - Drawings of Packaging Materials [DMPQ/CDRH]
- 3.2.P.8 Stability [OBRR]
- 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 & 5 mL) [DMPQ/OBRR/CDRH]
 - 3.2.P.2 Pharmaceutical Development [OBRR/DMPQ/CDRH]
 - Drug Product
 - Container Closure – System, Integrity Testing
 - 3.2.P.3 Manufacture
 - Manufacturing Site ((b) (4)) [DMPQ]
 - Batch Formula [OBRR]
 - Description of Manufacturing Process and Process Control [OBRR/DMPQ]
 - Control of Intermediates and Critical Steps [OBRR]
 - Process Validation [OBRR/DMPQ]
 - Process Validation – 2.5 mL Prefilled syringe
 - Process Validation – 5 mL Prefilled syringe
 - 3.2.P.5 Control of Drug Product [OBRR]
 - Release and Shelf Life Specifications
 - Batch Analyses
 - Characterization of Impurities
 - 3.2.P.7 Container Closure System [DMPQ/CDRH]
 - 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 [OBRR]
- 3.2.A Appendices
 - 3.2.A.1 Facilities and Equipment (Bayer – (b) (4)) [DMPQ]
 - Facilities and Equipment Summaries (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 and 5 mL pre-filled syringe
- 3.2.A.2 Adventitious Agents Safety Evaluation (Lyophilized Drug Product – Bayer) [OBRR]
 - 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) [OBRR]
 - TSE Assessment – Sterile Diluent pre-filled syringe

3.2.R Regional Information

- Executed Batch Records [OBRR]
- Method Validation Reports [OBRR] (Endotoxin, sterility – DMPQ)
- Shipping Study [DMPQ]
- Device Description – Vial Adapter [CDRH]
- Product Specification and Test Procedure – Vial Adapter [CDRH]
- Human Factor Study Report – Device [CDRH]
- Risk Management Report [OBRR/DMPQ]
- Device Description – Administration Set [CDRH]
- Product Specification and Test Procedure – Administration Set [CDRH]
- Device Description – Winged Infusion Set [CDRH]
- Drawing – Winged Infusion Set [CDRH]

3.3 Literature References [OBRR]

Module 4: Nonclinical Study Reports [OBRR]

- 4.2.1 Pharmacology
- 4.2.2 Pharmacokinetics
- 4.2.3 Toxicology
- 4.3 Literature References

Module 5: Clinical Study Reports [OBRR]

- 5.3.1 Reports of Biopharmaceutics Studies
- 5.3.3 Reports of Human Pharmacokinetic Studies
- 5.3.5 Reports of Efficacy and Safety Studies

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 #2: DMPQ IR for clarification on manufacturing activities at each facility site, contract test lab activities, identification of medical device manufacturers, comparison of facility areas and equipment used to produce Kogenate-FS and Kovaltry, and manufacturing plan to produce both Kogenate-FS and Kovaltry concurrently. (IR sent February 27, 2015; CBER Receipt date of Amendment, March 16, 2015; Sequence No. 0002)
- Amendment #26: DMPQ IR requesting equipment qualification reports, equipment cleaning reports, clarification on shared equipment for drug substance and drug product manufacture, media fill reports, procedures to control proposed (b) (4) step, correction to categorical exclusion for environmental assessment, and risk assessments for the drug product manufacturing process. (IR sent July 31, 2015; CBER Receipt date of Amendment, August 24, 2015; Sequence No.0025)
- Amendment #35: DMPQ IR requesting additional information on the shipping studies, quality control of failed sterile filter integrity test, and clarification on location of final packaging and labeling activities. (IR sent September 24, 2015; CBER Receipt date of Amendment, October 7, 2015; Sequence No. 0034)
- Amendment #46: DMPQ IR requesting clarification on the microbial load limits of the drug substance process. (IR sent February 12, 2016; CBER receipt date of Amendment, February 16, 2016; Sequence No. 0045)

Reviewer Recommendation: DMPQ recommends approval of this BLA for the new hemophilia A treatment product, Kovaltry, manufactured by Bayer Healthcare LLC. DMPQ did not identify outstanding facility or equipment issues that would preclude approval of this product.

REVIEW MEMO NARRATIVE

BACKGROUND

Bayer is seeking approval of a new recombinant human Factor VIII (rFVIII) product, identified as BAY 81-8973 or by the trade name Kovaltry. Kovaltry is a full-length recombinant human factor VIII protein, formulated with sucrose. Kovaltry has the same product formulation and active ingredient as the licensed product, Kogenate-FS (sucrose formulated). In addition, the two products have identical amino acid sequencing, same molecular formula, proteolytic processing, and similar post translational modification distribution (glycosylation and sulfation). The main differences between the two products arise from the improvements to the manufacturing process. For further details on the manufacturing differences, reference “Manufacturing Process Development” section in this memo.

The product is intended for the following clinical indications for adults and children with hemophilia A:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
- Control and prevention of bleeding episodes
- Peri-operative management (surgical prophylaxis)

(b) (4)

Kovaltry is not indicated for the treatment of von Willebrand disease.

The manufacturing process of Kovaltry was developed based on the current commercial Kogenate-FS manufacturing process, but includes significant changes and improvements in the Drug Substance

manufacturing process. The Drug Product manufacturing process is essentially the same as the current Kogenate-FS manufacturing process. Both the drug substance and drug product for Kovaltry will be manufactured in the same buildings as used for Kogenate-FS at Bayer's campus in (b) (4). The (b) (4) site is also responsible for labeling of the drug product, packaging of the finished goods into the market package, and for authorizing final release of the finished product.

In drug product form, the protein is stabilized in solution with excipients and lyophilized. The drug product is a sterile, lyophilized powder supplied in single use glass vials containing 250, 500, 1000, 2000, and 3000 International Units (IU). As with Kogenate-FS, Kovaltry requires reconstitution prior to administration to the patient. It is reconstituted with 2.5 mL sterile Water for Injection (sWFI) for the 250, 500, and 1000 IU sizes and with 5 mL of sWFI for the 2000 and 3000 IU sizes.

(b) (4) is responsible for the manufacture of the sterile WFI diluent which is supplied as a pre-filled syringe to Bayer. There are two packaging types for reconstitution using either an aluminum seal with plastic flip-off top and vial adapter or a reconstitution cap. Each packaging type connects to the sWFI pre-filled syringe.

Kovaltry is administered via intravenous interjection after reconstitution. Note, the administrative connections supplied with the drug product are the same connections as supplied with Kogenate-FS and are 510(k) approved. The review of the administration connections is the responsibility of OBRR and/or CDRH.

DMPQ elected to waive all inspections for this BLA as the Bayer site in (b) (4) sites in (b) (4) were all recently inspected (recent meaning within the last 2 years) and all had good compliance records. The inspection waivers can be referenced located in the EDR of the BLA.

MANUFACTURING SITES FOR KOVALTRY AND STERILE DILUENT

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

Bayer Healthcare LLC

(b) (4)

- Manufacture of drug substance and drug product (Kovaltry)
- Drug product release testing
- Labeling of drug product
- Incoming inspection of labeled sterile diluent syringes
- Packaging of finished goods (drug product, sterile diluent, administration kits) into market package
- Authorizes release of drug product and market packages
- Quality Control
- Stability storage and testing

(b) (4)

(b) (4)

Bayer (b) (4)

- Labeling of the 2.5 mL and 5.0 mL diluent syringe
- Release for final packaging at Bayer (b) (4)

MANUFACTURING PROCESS DEVELOPMENT

Bayer is approved for two rFVIII products, Kogenate (approved in 1993) and its sucrose-formulated successor Kogenate-FS (or rFVIII-FS) (also marketed as KOGENATE-FS Bayer, Helixate, Helixate FS, Helixate NEXGEN and Helixate M2V). Bayer states that in the 20 years since clinical testing for these products began, more than 8 billion IU have been administered.

Bayer is currently seeking approval for a new rFVIII product, which is identified as BAY 81-8973 or by the trade name, Kovaltry. Kovaltry is a new recombinant human FVIII product, with the same primary sequence as Bayer's currently licensed product. Kovaltry has the identical FVIII amino acid sequence, the same molecular formula, proteolytic processing and similar post translational modifications (glycosylation and sulfation) as Kogenate-FS.

The manufacturing process of Kovaltry was developed based on the current commercial Kogenate-FS manufacturing process, but includes significant changes and improvements in the Drug Substance manufacturing process. The Drug Product manufacturing process is essentially the same as the current

Kogenate-FS manufacturing process. Both the drug substance and drug product for Kovaltry will be manufactured in the same buildings as used for Kogenate-FS at Bayer's campus in (b) (4)

All clinical material was generated at full scale manufacturing capacity in licensed facilities and no scale-changes were made between clinical manufacturing and commercial (conformance lot) manufacturing.

DIFFERENCES BETWEEN KOVALTRY AND KOGENATE-FS MANUFACTURING

The following information summarizes the main drug substance manufacturing differences between the new product, Kovaltry, and the existing product, Kogenate-FS, which was used as the process model for the new product. In addition, this section also describes the process improvements for the manufacture of Kovaltry.

In order to improve the cell culture process, a new, higher producing and more robust clonal cell line was developed through co-transfection of cells from the Kogenate-FS working cell bank with human heat shock protein (HSP70). The new cell bank has increased productivity and shows increased resistance to programmed cell death (apoptosis).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The Kovaltry drug product manufacturing process steps are (b) (4) to the Kogenate-FS platform process with one minor adjustment. The difference between Kogenate-FS and Kovaltry drug product production is that Polysorbate 80 (b) (4) (b) (4) manufacture of Kovaltry, rather than during the (b) (4) step, as for Kogenate-FS. This helps simplifying the Kovaltry drug product manufacturing process by eliminating the additional step in Kogenate-FS process to adjust the Polysorbate 80 concentration in the (b) (4). The final concentration of Polysorbate 80 is comparable for the two drug products. All other drug product process steps, including sterile filtration and filling, are the same as the Kogenate -FS process.

DRUG PRODUCT DEVELOPMENTAL STUDIES

Bayer has completed studies to demonstrate that the drug product process based upon the Kogenate-FS process is suitable to manufacture Kovaltry. The down scale studies were provided in Section 3.2.P.2 Pharmaceutical Development of the BLA. The down-scale studies from each of the drug product process steps show that the product is consistently manufactured and is comparable to Kogenate-FS. DMPQ reviewed each of the studies and will comment only on the lyophilization down-scale study as this compared drying conditions and control limits. The remainder of the studies are product comparison and are the responsibility of OBRR to assess.

Lyophilization Down-Scale Study

The development study for the freeze-drying process included the characterization of the worst case process parameter operational limits. The study was designed to combine the control limits from each freeze-drying phase (b) (4) to generate (b) (4) extreme conditions as worst case scenarios. The extreme conditions were defined as those that were combined to give the (b) (4) and also, conversely, the (b) (4). The study compared the test results of the developmental batches to the interim clinical drug product release specifications.

The (b) (4) phase was tested with (b) (4)

(b) (4)

(b) (4)

(b) (4)


(b) (4)

(b) (4)


(b) (4)

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(b) (4)


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(b) (4)


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DRUG SUBSTANCE (KOVALTRY)

(b) (4)

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(b) (4)

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(b) (4)

(b) (4)

(b) (4)

DRUG PRODUCT (KOVALTRY)

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

Kovaltry is designed to have the same formula strengths, container/closure, and fill sizes (2.5 mL and 5 mL) as Kogenate-FS. The drug product consists of the rFVIII (active pharmaceutical ingredient), sucrose, histidine, glycine, sodium chloride, calcium chloride, and polysorbate 80.

There are two fill sizes of the final sterile filtered (b) (4) drug product that are used during production. The 2.5 mL nominal fill size produces vials of 250, 500 and 1000 IU nominal potencies (minimum batch size is (b) (4) vials; maximum batch size is (b) (4)0 vials). The 5 mL nominal fill size produces vials of 2000 and 3000 IU nominal potencies (minimum batch size is (b) (4) vials, maximum batch size is (b) (4)

vials (2000 IU potency) or (b) (4) (3000 IU potency). The same fill sizes are used for Kogenate-FS. The container/closure configuration for the drug product is a 10 mL colorless glass Type I (b) (4) vial with bromobutyl gray (b) (4) stopper for lyophilization. The same vial/stopper combination is used for Kogenate-FS. The reconstitution diluent is sterile water for injection. Note, the sterile water for injection will be covered in a separate section of this memo.

The drug product process includes the following steps: (b) (4) Each process step is described in further detail in the sections below.

PROCESS DESCRIPTION

The following is a description of the bulking and filling process of the drug product for Kovaltry. Note, this process is (b) (4) to the process for Kogenate-FS; the only difference being that Polysorbate 80 is added (b) (4) manufacture of Kovaltry, rather than during the drug product (b) (4) step, as for Kogenate-FS.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Information Request & Response (Amendment #35, Question #1): In your response dated July 31, 2015 to the information request dated June 29, 2015, you state in Table 1-27 Drug Product Process Attributes, that the sterile filter (b) (4) test is a critical process performance attribute and the (b) (4) is an action limit. Regarding your establishment of the sterile filter (b) (4) test as a process performance attribute, please address the following:

- a. Please describe the procedures you have in-place if the sterile filter does not meet the action limit. Please ensure your response explains the outcome of the lot (i.e. if the lot will be refiltered, rejected, etc.).

Response: The product sterile filtration is performed per approved operating procedures and Batch Production Records. The product is passed through (b) (4) (designated as (b) (4)

- b. Please explain the controls you have in-place if (b) (4) does occur in order to prevent contamination.

Response: Sterile (b) (4) of the product is not allowed and no further production is performed if the sterile filter does not pass (b) (4) testing.

- c. Please explain if retesting of the filter is permitted based upon your procedures.


Response: Re-testing of the filter is allowed, and (b) (4) can be retested once, as described in item a) above.

Reviewer Comment: The filter can be retested per protocol; however, the product is not permitted to be (b) (4) if the sterile filter does not pass (b) (4) testing as described. The response is adequate and no further follow-up is needed.

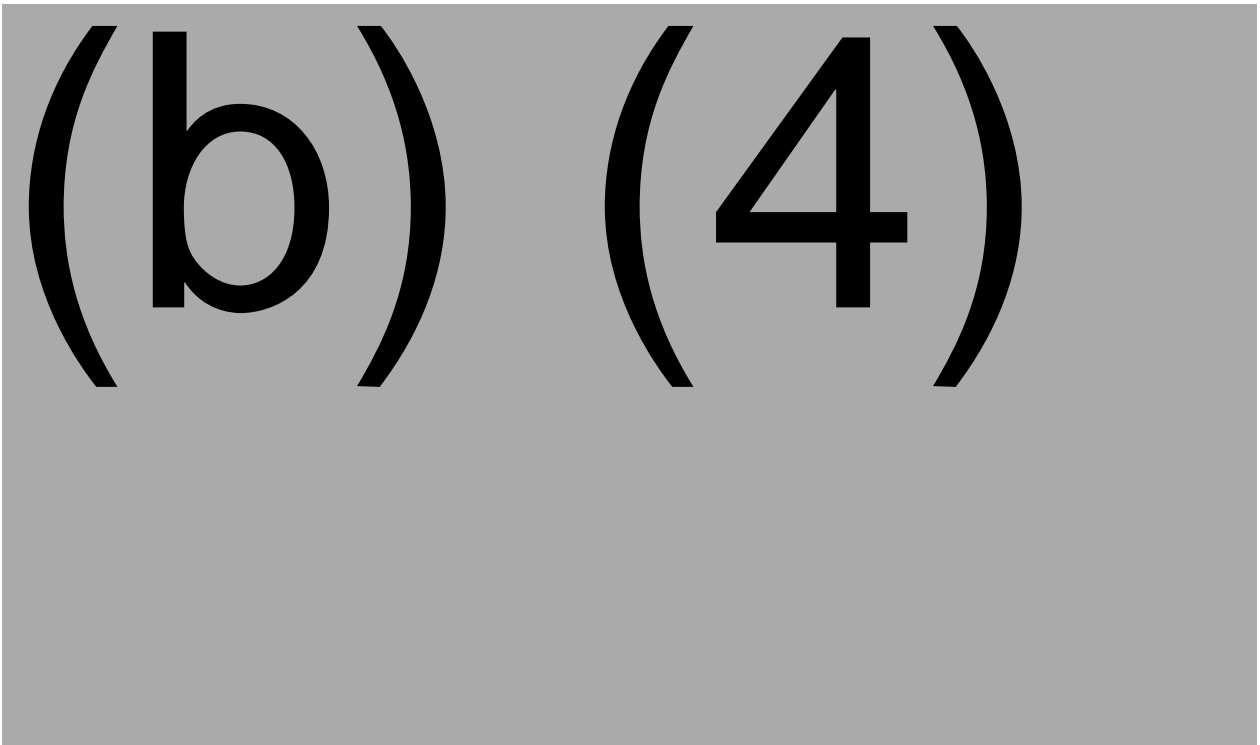
PROCESS VALIDATION

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: (b) (4) formulation, filling, freeze-drying, and vial capping.

(b) (4)

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(b) (4)

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

(b) (4)

(b) (4)

DRUG PRODUCT SPECIFICATIONS & BATCH ANALYSES

The following table provides a summary of the drug product specifications for Kovaltry. Note, the potency is dependent upon the final target of the vial size. The table shows a range which covers the product potency from 250 IU to 3000 IU.

Table 11: Kovaltry Drug Product Specifications

Parameter	Specification
Appearance before reconstitution	White to slightly yellow solid
Appearance after reconstitution	Liquid is clear, colorless with no particles present
Clarity	(b) (4)
Color	(b) (4)
Identity (b) (4)	(b) (4)
Solubility time	(b) (4)
pH	6.6 – 7.0
(b) (4)	(b) (4)
Moisture	(b) (4)
Glycine	(b) (4)
Sodium	(b) (4)
Calcium	(b) (4)
Histidine	(b) (4)
Sucrose	(b) (4)
Polysorbate 80	(b) (4)
Purity (b) (4)	(b) (4)

The analytical tests that are performed on the drug product along with the validation of the methods are the responsibility of DBSQC to perform. This includes the review of the endotoxin and sterility test methods and method validation.

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 Kovaltry at the Bayer (b) (4) facility in Building (b) (4) Sterile Fill & Finish Facility. Note, all equipment is multi-product use and is also used in the manufacture of Kogenate-FS and the IND product (b) (4).

This section will provide a description of the equipment qualification that was performed. Regarding the equipment qualification, Bayer states that the qualification of the process equipment included performing IQ/OQ/PQ which included confirming operation with the control systems, calibration, confirming operation within intended range, verification of load patterns, and demonstrating consistency of performance within the specified operating ranges. For some of the major pieces of equipment, further details regarding the equipment qualification are requested.

Also, this section of the memo will cover the cleaning validation that was performed for each major piece of equipment. Bayer states that cleaning validation was performed on product contact equipment and that the cleaning validation strategy required (b) (4) successful runs to verify effective removal of soil and cleaning agents. A grouping strategy was used to cover multiple pieces of equipment of the same type within a group. The assessment of cleaning was analyzed through (b) (4). The unclean equipment hold times and clean equipment hold times were established in the studies. For some of the major pieces of equipment that are shared between Kovaltry, Kogenate-FS, and the IND product, further details regarding the cleaning validation and the results of the cleaning validation are requested. Bayer stated that the cleaning process is the exact same for Kovaltry as is validated for Kogenate-FS.

Note, the major pieces of equipment used in the drug product process are underlined in the summary below. All drug product equipment is shared between Kogenate-FS, Kovaltry, and IND (b) (4).

(b) (4)

Equipment Qualification

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

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.

- (b) (4)

Equipment Qualification

The (b) (4) and the associated (b) (4) were qualified to ensure the effective (b) (4) of vials prior to (b) (4).

Cleaning Validation

(b) (4) and the (b) (4) used for (b) (4) were evaluated for (b) (4) on vial surfaces to demonstrate the effectiveness of the (b) (4) and the (b) (4).

- (b) (4)

Equipment Qualification

A (b) (4) cycle was developed and qualified to ensure effective (b) (4) of vials prior to filling. (b) (4) vials were used to show acceptable temperature distribution and to verify that a (b) (4) reduction of (b) (4) vials is achieved.

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 qualified for Kogenate-FS and the equipment was not modified for the Kovaltry process. In addition, both Kogenate-FS and Kovaltry products use the same vials.

Filling Equipment

- Vial Filling/Stoppering Machine: The filling/stoppering machine is located in a Grade (b) (4) area. A transfer system allows aseptic delivery of sterile stoppers from the surrounding Grade (b) (4) area. The fluid path components, including (b) (4), are (b) (4) and (b) (4) from the (b) (4). The filling equipment (b) (4) checks the weight of the filled vials (every (b) (4) vials).

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: Bayer notes that the filling equipment was qualified for the manufacture of Kovaltry; however, DMPQ requested the results of the PQ of this qualification for further review. Also, as part of the process validation of the filling process, Bayer has performed (b) (4) media fills to demonstrate the filling process is performed in accordance with aseptic technique. DMPQ also requested a copy of the media fill results from the longest duration media fill that was performed. Based upon the review of the media fill results and the equipment qualification of the filling machine, sufficient data was provided to DMPQ to ensure that the filling equipment has been properly qualified for use in the manufacturing process of Kovaltry and that

the filling equipment is used in a sterile manner to ensure a sterile product. Also, it is noted that the filling equipment performs an (b) (4) on the (b) (4) vial to ensure proper filling weight. If an issue regarding the filling equipment was to occur, it would likely be detected at this filling weight check.

Information Request: Please provide the results of the performance qualification for the vial filling machine in which you demonstrate the filling process of Kovaltry. Please ensure the response contains a summary of the acceptance criteria and results of the qualification.

Response (Amendment #26, Question #11): Bayer explained that the filling process of Kovaltry was demonstrated by conducting the (b) (4) (as noted previously, every (b) (4) vial is checked to ensure correct (b) (4) during routine filling operations). The (b) (4) was previously qualified for the 2.5mL and 5.0mL fill sizes for the Kogenate-FS process. The Kovaltry process utilizes the same (b) (4) as the Kogenate-FS process and does not require additional testing. The (b) (4) is performed by processing vials through the filling/stoppering machine as its validated maximum and minimum operating speeds. The In-Process-Control (IPC) system periodically (b) (4).
Acceptance of the qualification is measured by (b) (4).
Filling challenge tests were also conducted to simulate equipment stops to capture any changes to filling accuracy over extended stop times.

Reviewer Comment: From the response, the filling machine has been adequately qualified for use in the Kogenate-FS process and therefore is acceptable to be used to fill the Kovaltry product. No further issues remain regarding the qualification of the fill machine or the filling process.

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) were used to qualify the (b) (4) cycle to show acceptable (b) (4) and to verify acceptable reduction in viable organisms.

Information Request: Please provide a summary of the cleaning validation and of the sterilization validation that were performed for the product contact filling equipment. Please include the acceptance criteria and results from the three run validation in which you demonstrate the cleaning process is suitable to remove product residue and cleaning agents from this product contact equipment. Regarding the sterilization cycle of the filling equipment, please provide a diagram showing the location of the thermocouples and biological indicators and your rationale for the placement of these items. In addition, please provide the acceptance criteria and results from the sterilization validation.

Response (Amendment #26, Question #12):

The vial filling/stoppering machine used in the Kovaltry drug product manufacturing process is cleaned per an automated (b) (4) consists of (b) (4). The cleaning

[illegible]

The PQ verified that the (b) (4) cycle for the filling and stoppering machine, operating under worst-case conditions, i.e. a (b) (4) than used during production, is able to effectively and reproducibly achieve the qualification acceptance criteria. The locations were chosen based on (b) (4) that were determined during the Engineering Test Plan, temperature and pressure monitoring locations, distance from the steam source, and to sufficiently map all drain lines. For each of the PQ runs, the cycle was aborted after all (b) (4) accumulated a minimum (b) (4) minutes. The (b) (4) for the Vial Filling/Stoppering machine is routinely re-qualified using (b) (4) criteria.

Freeze-Drying Equipment

- 70

(b) (4) with no operator interventions required during operation. The lyophilizers undergo (b) (4) prior to each processed batch.

The same lyophilizers that are used for Kogenate-FS will be used for Kovaltry. The equipment qualifications for the lyophilizers have not changed due to the introduction of Kovaltry. The cleaning and sterilization processes for the lyophilizers has not changed due to the introduction of Kovaltry; the process are the exact same as for Kogenate-FS. In order to demonstrate the cleaning process can adequately remove Kovaltry, a (b) (4) cleaning validation run was performed as described in the section below.

Equipment Qualification

Shelf temperature mapping was performed to demonstrate that the temperature of the shelves is maintained within a design range around the process set-point. (b) (4) were used for temperature mapping. Shelf temperature mapping was performed to demonstrate that the temperature of the shelves is maintained within a design range around the process set-point. (b) (4) were used for temperature mapping.

Information Request: For the temperature mapping study that was performed for the lyophilizer, please provide a summary of the study along with the acceptance criteria and results demonstrating that the lyophilizer maintains proper temperature within the chamber. In addition, please provide a diagram of the placement of the (b) (4) in the lyophilizer and the rationale for the placement of the (b) (4). Please indicate if the study was performed using Kovaltry or an equivalent placebo product.

Response (Amendment #26, Question #13):

Bayer explained that the (b) (4) lyophilizers used to freeze-dry the Kogenate-FS and Kovaltry products have been qualified for use and that temperature mapping studies have been for the Kogenate-FS product. Following the temperature mapping study, Bayer then performed a product thermal mapping study using Kogenate-FS. The two fill sizes (2.5 mL and 5.0 mL) were each challenged at the minimum and maximum load configurations with no less than (b) (4) run each per lyophilizer.

Note, as the Kovaltry product is an equivalent product to Kogenate-FS (i.e. same active ingredient), the temperature mapping study and the product thermal mapping study conducted for Kogenate-FS apply to Kovaltry.

Reviewer Comment: Based upon the response from Bayer, the temperature mapping study and thermal mapping study performed for Kogenate-FS are acceptable to provide a uniform lyophilized product throughout the chamber. Because the two products are similar, the lyophilizer is qualified for use in the manufacture of the Kovaltry drug product and no additional studies are required to be completed.

Cleaning Validation

Cleaning and Sterilization cycles were qualified utilizing (b) (4) systems. Cycles were defined and qualified to ensure sterility of the lyophilizers following a lyophilization cycle and before the product enters the freeze dryer. (b) (4) were used to qualify the

(b) (4) cycle to show acceptable steam penetration and to verify acceptable reduction in viable organisms.

Information Request: Please provide a summary of the cleaning and sterilization cycles of the lyophilizer. Regarding the cleaning validation of the lyophilizer, please provide a summary of the results and the acceptance criteria demonstrating that the cleaning process is effective to remove trace residue of Kovaltry. For the sterilization validation of the lyophilizer, please the results of the along with the acceptance criteria. In addition, please provide a diagram showing the placement of the (b) (4) and your rationale for the placement of these items in the lyophilizer.

Response (Amendment #26, Question #14): The (b) (4) lyophilizers used in the freeze drying process of the Kovaltry drug product are cleaned per an (b) (4) cycle. A (b) (4) is utilized for automated cleaning of the lyophilizers. The (b) (4) cycle consists of the following steps and delivers the cleaning solution (b) (4) per programmed set-points.

- (b) (4)

The lyophilizer cleaning method was originally validated with (b) (4) successful cleaning validation runs (b) (4) runs per lyophilizer) using both Kogenate-FS and (b) (4) in combination as a worst-case soil challenge. Conditions were chosen to represent both routine production runs and media fills. Kogenate-FS was applied to the lyophilizer shelves, followed (b) (4) Following the (b) (4), a (b) (4) cycle was executed.

This same cleaning method was confirmed to be acceptable for Kovaltry with (b) (4) additional cleaning validation run using Kovaltry as the soilant. For this run, the same execution conditions were applied. Effectiveness of the cleaning cycle to remove soilant and/or product residue and cleaning agents to acceptable levels was demonstrated through analysis of rinse and surface swab samples and visual inspection against acceptance criteria which are the following:

Test	Acceptance Criteria
(b) (4)	

(b) (4)

(b) (4). All results of the cleaning validation run met the criteria. The cleaning validation of the lyophilizers verified that cleaning procedures are consistent and reliable.

The (b) (4) lyophilizers used in the freeze drying process of the Kovaltry drug product are (b) (4). The PQ demonstrated the efficacy of the (b) (4) cycle and determined the minimum validated (b) (4) for the product lyophilizers located in Building (b) (4). The placement of the (b) (4) were based on (b) (4).

Additional locations were selected to provide full monitoring of the system, and to verify that (b) (4) conditions were met. The (b) (4) was qualified using (b) (4).

The lyophilizer (b) (4) cycles for the lyophilizers are routinely re-qualified using (b) (4) challenge criteria.

Note, the sterilization process of the lyophilizers is the same for both Kogenate-FS and Kovaltry. The (b) (4) cycle did not require requalification due to the introduction of Kovaltry.

Capping Equipment

- Automated capping equipment is used to apply an aluminum overseal or reconstitution cap to fully stoppered vials. Aluminum overseals are applied in Grade (b) (4). Reconstitution caps are applied in Grade (b) (4). A (b) (4) is used to transfer reconstitution caps from the Grade (b) (4) into the Grade (b) (4) area.

Equipment Qualification

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

Process Support Equipment

- (b) (4)

Equipment Qualification

Load configurations were defined and qualified to demonstrate effective steam penetration and sterilization. (b) (4) were used to show acceptable steam penetration and to verify acceptable reduction in viable organisms.

Information Request: Regarding the autoclave which is used to sterilize product contact filling equipment, please confirm if there have been any changes to the qualified load patterns resulting

from the introduction of Kovaltry. If so, please provide a summary of the new load pattern, including a diagram with the placement of the (b) (4), and results of the qualification showing a reduction in organisms of the load items.

Response (Amendment #26, Question #15): Bayer confirms there were no changes to the qualified autoclave sterilization loads resulting from the introduction of Kovaltry.

Reviewer Comment: As the load patterns have not changed due to the introduction of Kovaltry, the qualification of the autoclave did not require review.

(b) (4)

(b) (4)

(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 one minor process difference, the drug product processes of Kogenate-FS and Kovaltry are (b) (4). The same facility and equipment are used to produce the drug products of Kogenate-FS and Kovaltry. 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

The container closure system for Kovaltry consists of a vial, stopper, and either a reconstitution cap or overseal. Kovaltry utilizes the platform container and closure system developed for Kogenate-FS with an identical vial, stopper, aluminum seal or reconstitution cap, and an identical Instruction for Use and dosing procedure.

The container for Kovaltry is a 10 mL glass vial with colorless glass, type I, and (b) (4). The vial is supplied by (b) (4). The stopper is a gray bromobutyl rubber, (b) (4) coated, (b) (4), suitable for lyophilization processes. The stopper is supplied by (b) (4). 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.

Container Closure Integrity Testing

The container closure system and secondary packaging system were selected in order to provide adequate protection from light, moisture, and gas permeation. In total, three aspects of container closure functionality were evaluated including: needle force activation (CDRH), container closure integrity (DMPQ), and protection against environmental stress and contamination during long term storage (OBRR).

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

The validation of the container/closure configuration was carried out with aluminum overseals. The stoppers and vials used in the study were processed (sterilized, filled, and capped) per approved batch production records and standard operating procedures. (b) (4) were filled into the vial/stopper combination with the aluminum overseals.

(b) (4)

A second container closure integrity test was performed using the reconstitution caps. The stoppers and vials used in the study were processed (sterilized, filled, and capped) per approved batch production records and standard operating procedures. (b) (4) were filled into the vial/stopper combination with the reconstitution cap.

(b) (4)

Reviewer Comment: The information regarding the results of (b) (4) test did not describe the preparation of the positive controls or the identification of the limit of detection. Further details regarding the container closure testing were needed to assess the suitability of the test procedure.

Information Request: Regarding the (b) (4) testing that you performed to demonstrate container closure integrity using the reconstitution cap and the aluminum overseal, please provide the complete report and the protocol for this testing. Please ensure the report or protocol describes the preparation of the positive control and establishment of the limit of detection.

Response (Amendment #26, Question #16): Bayer explained that the positive control was prepared by (b) (4). In order to establish the limit of detection, a (b) (4) of an (b) (4). The detection limit was determined by (b) (4).

In the response, Bayer also provided a copy of the report and protocol as requested. The (b) (4) study was completed by (b) (4) for Bayer. The protocol and report confirmed the information provided by Bayer in the response. The response was adequate and provided the information that was needed in order to complete the review; no further issues remain regarding container closure integrity of the drug product.

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).

For the reconstitution cap, Bayer performs a dimensional inspection to ensure measurements are within specified tolerances, component check to confirm presence of all components, and review of the (b) (4) testing.

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

MEDICAL DEVICES

There are two packaging combinations for Kovaltry:

- Kovaltry drug product vial with a reconstitution cap, diluent pre-filled syringe, and an administration set
- Kovaltry drug product vial with an aluminum overseal, diluent pre-filled syringe, vial adapter, and an administration set

The reconstitution cap, vial adapter, and administration set are classified as medical devices. CDRH was included in the review committee for this BLA to review the information provided, such as the risk assessments and human factor studies, regarding the medical devices and to ensure compliance with 21 CFR 820. Bayer explains that the same medical devices are used for Kogenate-FS.

Note, A review of the safety of the container closure system is the responsibility of OBRR or CDRH to assess. The use of the administration set for drug delivery is the responsibility of OBRR or CDRH to assess. In addition, CDRH is responsible to assess the human factors study for the use of the delivery devices and to assess the devices met the requirements of 21 CFR 820.

Reconstitution Cap

The reconstitution cap is used as an integral part of the product vial, functioning as both a cap and a needle-free reconstitution/liquid transfer device. This device replaces the standard needle and syringe approach for reconstitution. The usability, safety and effectiveness of the platform primary container closure system and the reconstitution cap have been successfully demonstrated with Kogenate-FS in the marketplace and with Kovaltry during clinical studies.

The reconstitution cap contains a cap, a base and a needle/luer assembly. The cap and the base are constructed of (b) (4). The needle/luer assembly is constructed of a (b) (4). The reconstitution cap is attached to the base during the (b) (4). The manufacturer pre-sterilizes the reconstitution cap by (b) (4). The sterilization dose was established and the sterilization process was developed, validated and controlled in accordance with ISO standards.

The manufacturer of the reconstitution cap is Baxter LTD/Biodome and has an approved Drug Master File (DMF) (b) (4).

For the use with Kovaltry, Baxter completed a design Failure Mode and Effects Analysis of the reconstitution device and did not identify a design-related risk for the user. A risk assessment of the manufacturing process was performed and risks were mitigated in process validation measures.

Based upon the risk assessment conducted and the review of compliant data for Kogenate-FS which has the identical reconstitution cap, the remaining usability risks are acceptable.

Reviewer Comment: As the cap has an approved DMF and is approved for use with Kogenate-FS which has the same vial/stopper combination as Kovaltry, DMPQ has no review items for this component and the risk assessments are deferred to CDRH for review.

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.

A Human Factors Study was performed for the reconstitution process using the vial adapter. The study evaluated whether users could effectively reconstitute and administer Kovaltry without performing preventable user errors that would result in harm, confusion, or safety risks. Note, CDRH is to review the Human Factors Study.

In addition, a device risk assessment was performed for the vial adapter to demonstrate that there are no design-related risks for the user in the intended way of use (i.e. reconstitution and administration).

Reviewer Comment: As the vial adapter is 510(k) cleared and is in use with Kogenate-FS, DMPQ does not have any review issues regarding the vial adapter. The Human Factor Study and the design risk assessment are the responsibility of CDRH to review.

Administration Sets

There are two administration sets for the drug delivery. The first set, administration set (b) (4), is manufactured by (b) (4), and is 510(k) cleared.

The second set, administration set (b) (4), is manufactured by (b) (4) and is 510(k) cleared.

Both sets have a polyvinyl chloride (PVC) tube equipped with a stainless steel cannula, Luer adapter, integral filter, and wings. Drawings of the devices were provided in the BLA.

Reviewer Comment: As the administration sets are 510(k) cleared and are used for drug delivery administration with Kogenate-FS, DMPQ has no review issues regarding administration sets. Review of the sets, if warranted, is deferred to CDRH.

FACILITY DESCRIPTION: BAYER (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)

- Storage of raw materials and in-process materials at ambient, 2-8°C, and/or frozen conditions.

Building (b) (4)

- Storage of master and working cell banks

Building (b) (4)



Building (b) (4) Warehouse, Packaging

- Storage of raw materials and in-process materials at (b) (4) conditions.

- (b) (4)

(b) (4)

- Filling of sterile-filtered bulk into vials in aseptic processing area
- Freeze-drying of filled vials
- Capping

Buildings (b) (4)

- Analytical testing laboratories

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, Clinical product – seeking licensure (subject of this BLA)
- IND product (b) (4)

All three products are recombinant DNA-derived therapeutic proteins, originating from the same parental cell line, baby hamster kidney cells. All three products are lyophilized and require reconstitution for intravenous injection.

Building (b) (4) Drug Substance

The products are manufactured on concurrent manufacturing schedules in Building (b) (4). Building (b) (4) is comprised of (b) (4) plants, (b) (4), each of which consists of (b) (4) has (b) (4) suites and (b) (4) has (b) (4) suites. The following table describes the activities for each product that are manufactured in the different plants.

(b) (4)

(b) (4)	(b) (4)
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(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 Table 12.

In the following suites in (b) (4): the (b) (4) suites there is no product contact equipment that is shared between the licensed product, Kogenate-FS, and the proposed product, Kovaltry. In the (b) (4) suites of (b) (4) the following product contact equipment is shared between the licensed product, Kogenate-FS, and Kovaltry:

(b) (4)

Additionally, cleaning validation is performed for all shared product-contact equipment. The cleaning validation methodology for cleaning Kovaltry and IND product (b) (4) from all the shared equipment is planned and conducted concurrently during clinical manufacturing utilizing the equipment soiled during production.

Information Request: Please provide a list of all shared drug substance equipment between Kogenate-FS, Kovaltry and IND product (b) (4). For the equipment that is shared, please describe the procedures you have in-place to prevent cross-contamination.

Response (Amendment #26, Question #5): In the response, Bayer clarified that there is no product contacting equipment in the (b) (4). In the (b) (4) the following drug substance equipment is shared between all three products:

- (b) (4)

Additionally, the following equipment is shared between Kovaltry and IND product (b) (4) in the (b) (4)

(b) (4)

The (b) (4) are not utilized for the manufacture of Kogenate-FS; the suites will be used for Kovaltry and IND (b) (4), in which the following equipment is shared:

- (b) (4)

Appropriate controls are employed to prevent cross-contamination during concurrent production and product change-over. The design of the facility and the equipment in conjunction with production scheduling (campaigning and/or segregation of activities/products), documentation, equipment use procedures and validation programs ensure that multiple products can be manufactured in the facility in accordance with current good manufacturing practices (cGMP).

A risk-based approach is taken with regard to new product introductions and risk assessments are routinely performed and documented. Prior to introduction of a new product, the Master Cell Bank must meet the pathogen safety requirements outlined in ICH Q5A, and ICH Q5D. Since the production activities in (b) (4) include both pre-viral and post-viral processes, existing mitigations measures in place include steps to minimize any potential for viral cross-contamination as well.

Contamination/Cross-Contamination Controls

As Building (b) (4) is a multi-product facility, Bayer has implemented procedural controls to minimize or reduce the chance for contamination or cross-contamination. A summary of the contamination controls is provided below.

Facility Control

- (b) (4)

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., gowning, degowning). The AHUs are (b) (4)

(b) (4)

(b) (4)

Personnel Flow

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.

Material, Product, Equipment and Waste Flows

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:

- Room Utilization (b) (4) floors
- Personnel Flow Diagrams (b) (4) floors)
- Equipment Flow (b) (4) floors)
- Raw Material Flows (b) (4) floors)
- Solid Waste Flows (b) (4) floors)
- Media Flow (b) (4) floors)
- Cell Flow (b) (4) floors)
- Intermediate Flow (b) (4) floors)

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 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 facility is used for the manufacture of Kogenate-FS, licensed product, the establishment of the facility cleaning schedule and demonstration of facility cleaning effectiveness is covered under the surveillance inspection for Kogenate-FS. No review issues are noted regarding facility cleaning.

Manufacturing Process Control

- Manufacturing documents (MBRs, EBRs, and SOPs) are in place to address segregation procedures, personnel/material flow, equipment/area cleaning, changeover/area clearance and preventive maintenance
- Product specific EBRs and work instructions
- Only one product manufactured at a time in each suite
- Product changeover required to transition between products
- Entrance to suites labeled with product being processed
- Risk Assessments are in-place to address drug substance product changeover and to mitigate potential cross-contamination
- Standard Operational Procedures for personnel gowning and flow, facility/equipment changeover/cleaning, and raw material and drug substance product flow are in-place to prevent cross-contamination

Inventory Control

The (b) (4)

[REDACTED]

Drug Substance Process Flow

(b) (4)

[REDACTED]

(b) (4)

[REDACTED]

(b) (4)

(b) (4)

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 drug product for the licensed product, Kogenate-FS, for the proposed product, Kovaltry, and for the clinical product, (b) (4). Concurrent production schedules are used for production of the drug product in this building. Building (b) (4) is a (b) (4) building consisting of (b) (4) and an (b) (4).

The design of the facility and the equipment in conjunction with production scheduling, documentation, equipment use procedures and validation programs ensure that multiple products can be manufactured in the facility in accordance with cGMPs.

A risk-based approach is taken with regard to new product introductions and risk assessments are routinely performed and documented. Prior to introduction of a new product, the Master Cell Bank must

meet the pathogen safety requirements outlined in ICH Q5A, and ICH Q5D. Since all production activities in Building (b) (4) are (b) (4), the existing mitigations measures that are in-place, minimize any potential for cross-contamination.

Additionally, cleaning validation is performed for all shared product-contact equipment. The following product contact equipment is shared between the licensed product, Kogenate-FS, and Kovaltry:

- (b) (4)

The cleaning validation methodology for cleaning Kovaltry and IND product (b) (4) from all the shared equipment was conducted concurrently during clinical manufacturing utilizing the equipment soiled during production and shown to be effective.

Information Request: As your drug product equipment is shared between Kogenate-FS (licensed product), Kovaltry (subject of this BLA), and an IND product, (b) (4), please describe the procedures you have in-place to prevent cross-contamination between the different products. Also, please explain if you have completed a risk assessment of the cleaning process between the three different products. If so, please provide a copy of this risk assessment in which you demonstrate the mitigation of the product contamination between the shared equipment.

Response (Amendment #26, Question #9): In the response, Bayer explained that Building (b) (4) has been designed to operate as a multi-product facility. The drug products of Kogenate-FS, Kovaltry, and IND product (b) (4) are similar at the (b) (4) step and therefore, the use of the facility to allow production of the multiple products requires no procedural changes. The validated cleaning procedures for Kogenate-FS have been validated for the cleaning of Kovaltry and IND (b) (4). Bayer also explained they performed a risk assessment to manufacture the multiple products in Building (b) (4), the risk assessment is titled, "Risk Assessment for Filling and Freeze Drying Process Changeover of Kogenate-FS, Kovaltry, and IND (b) (4) in Building (b) (4), Document No. R-000-04-025. The risk assessment identified all risks as low with existing measures in place. The current cleaning and sanitization procedures at current frequencies adequately control the cleaning of equipment and cross-contamination between product lots, regardless of product type. Bayer also included in their response a summary of their contamination controls which was as described in the BLA and is summarized below.

Contamination/Cross-Contamination Controls

Building (b) (4) is the sterile filling facility for rVIII products including: Kogenate-FS (licensed), Kovaltry (subject of this BLA), and IND product (b) (4). The building is designed to assure aseptic processing in order to consistently produce a sterile product. Bayer has implemented the following controls to minimize or reduce the chance for contamination or cross-contamination.

Contamination Control mitigation practices:

- Environment
 - Sterile product is exposed only to Class (b) (4) environment within a Class (b) (4) background

- Directional airflow cascades from Class (b) (4) to Class (b) (4) to Class (b) (4) areas
- Differential pressure is maintained between rooms of different classification
- Environmental monitoring confirms that (b) (4) for each area classification are maintained
- Personnel
 - Personnel gowning is class-specific
 - Personnel are trained, qualified, and monitored for aseptic technique
- Workflow and Access Control
 - Personnel and material flows are optimized to reduce the potential for contamination
 - Personnel and materials flow (b) (4) from Class (b) (4) to the Class (b) (4) area with electronic access for security
 - Gowning and material pass-through rooms are (b) (4)
 - Soiled parts and equipment are (b) (4)
 - Major process steps are automated to reduce operator handling and intervention
- Cleaning and Sanitization
 - Equipment and facility cleaning procedures are validated
 - Sterile product path and associated connections are (b) (4), alleviating the need for aseptic connections
- Manufacturing Process Control
 - Procedures are in-place addressing segregation, personnel/material flow, equipment/area cleaning, changeover, area clearance, and preventive maintenance
- Inventory Control
 - Usage of raw materials, intermediates, or drug substances is controlled by an inventory control system in combination with a predefined recipe

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 (b) (4)

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

The Class (b) (4) environments are (b) (4)

Reviewer Comment: As the same building and areas are used to produce the drug product for Kogenate-FS (licensed product), 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 Team Biologics 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) to (b) (4) .

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) sanitized.

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) 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:

- Room Utilization (b) (4) floors
- Personnel Flow Diagrams (b) (4) floors)
- Raw Material Flows (b) (4) floors)
- Waste Flows (b) (4) floor)
- Component Flow (b) (4) floors)
- Product Flow (b) (4) floor)

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 Kogenate-FS, licensed product, the establishment of the facility cleaning schedule and demonstration of facility cleaning effectiveness is covered under the surveillance inspection for Kogenate-FS. No review issues are noted regarding facility cleaning.

Inventory Control

The drug products are (b) (4). 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 (b) (4) manufactured (b) (4) in each of the processing areas:

- a) (b) (4)
- b) (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 for Kogenate-FS, Kovaltry, and IND product (b) (4).

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 minus testing for (b) (4).

In Building (b) (4) the (b) (4). In Building (b) (4), the clean (b) (4). Bayer performs (b) (4) testing on the (b) (4).

Bayer states that the utility system for WFI and clean steam 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), and (b) (4).

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

Waste

Liquid waste from production is (b) (4)

Reviewer Comment: As the manufacture of Kovaltry is occurring in the same buildings as the licensed product, Kogenate-FS, the Team Biologics 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 Team Biologics inspection for Kogenate-FS.

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.

Environmental Monitoring

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

(b) (4)

Routine EM of (b) (4)

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 manufacturing process and the same monitoring frequency and monitoring types will be in use during the manufacture of Kovaltry. No review issues are noted in the review of the environmental monitoring plans for Kovaltry.

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 IND product (b) (4). 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, 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 Kovaltry.

STERILE DILUENT

The sterile water for injection (sWFI) diluent which is used for reconstitution of the Kovaltry drug product is manufactured by (b) (4). The diluent is supplied as a prefilled syringe. Two sizes of the sterile diluent, 2.5 mL and 5.0 mL, are used for the reconstitution depending upon the concentration of the drug product to be reconstituted. Bayer also uses (b) (4) to produce the sterile diluent for the currently licensed Kogenate-FS product. Bayer confirms in Amendment #2 response to Question #3 that the manufacturing processes for the unlabeled diluent products, 2.5 mL and 5.0 mL, are (b) (4) for the Kogenate-FS and Kovaltry products.

The following is a summary of the (b) (4) facility sites in which certain aspects of the manufacturing and testing of the sWFI diluent occur.

(b) (4)

(b) (4)

(b) (4) is responsible for performing release testing of the sterile diluent. The Bayer (b) (4) site located in (b) (4) is responsible for the labeling and assembly of the sWFI diluent syringe, warehousing of the syringe, and for the release of the syringe to final packaging/market. These same activities for the diluent occur at Bayer's facility in (b) (4) for the Kogenate-FS product.

DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

The following summarizes the manufacturing process and process controls for the manufacture of the sWFI diluent produced by (b) (4). The maximum batch size for the 2.5 mL size is (b) (4) prefilled syringes and the max batch size for the 5.0 mL size is (b) (4) prefilled syringes.

Water for Injection is prepared from Purified Water by (b) (4)

Chemical and microbiological testing is performed according to a defined schedule and according to (b) (4) requirements. WFI for compounding is tested (b) (4) (when compounding is performed) for (b) (4) and (b) (4) for additional tests according to (b) (4)

(b) (4)

(b) (4)

CONTAINER INFORMATION/CONTAINER CLOSURE INTEGRITY

The container for the 2.5 mL sWFI is a clear, colorless, (b) (4) glass, Type (b) (4) 3 mL syringe. The nominal overfill is (b) (4)/syringe. The container for the 5.0 mL sWFI is a clear, colorless, (b) (4) glass, Type (b) (4) 5 mL syringe. The nominal overfill is (b) (4)/syringe. Both the plunger stopper and tip cap stopper are a grey (b) (4) rubber.

Container closure integrity was assessed by (b) (4) testing of single and double sterilized syringes for both 2.5 mL and 5 mL fill sizes. The results of the (b) (4) test are summarized below.

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment: The results of the (b) (4) test demonstrate the container closure integrity of the sWFI diluent prefilled syringe.

STABILITY

Stability results of the 2.5 mL and 5 mL sWFI diluent prefilled syringes manufactured by (b) (4) are provided in the BLA which cover a storage period of up to (b) (4) at the recommended storage temperature (b) (4) and at the (b) (4) storage conditions for more recent batches.

Results accumulated to date on the 2.5 mL and 5 mL SWFI (b) (4) batches meet the stability requirements and continue to support the approved shelf life claim for the full dating period of (b) (4)

Note, It is the responsibility of OBRR to review the stability results.

Reviewer Comment: DMPQ does not have any review issues with the manufacture of the sWFI diluent produced by (b) (4)

FINAL LABELING & PACKAGING

The labeling of the drug product container is performed by Bayer at their facility in (b) (4). The labeling of the sterile WFI diluent is performed by Bayer at their facility in (b) (4). After the diluent is labeled, it is then shipped to Bayer (b) (4) for final packaging. Upon receiving the labeled diluent syringes from Bayer (b) (4), Bayer (b) (4) performs incoming inspection on the syringe before they are released for final packaging. The Bayer (b) (4) site performs the final packaging of the market packages which consists of the drug product, sterile diluent, administration kit, and product insert. The packaging process is similar to the packaging process for Kogenate-FS minus the product specific differences such as the label and product insert.

The final packaging process is conducted on an (b) (4) packaging line with concurrent equipment operation as an integral system in a continuous process. These operations include labeling, carton formation, component insertion, carton sealing, weighing, carton printing, case packing, and case

labeling. The final container vials are loaded into the individually partitioned sections within the case. After the final containers are packed, another layer of padding is placed on top of the final containers and the shipping case is sealed. A case label is then applied to the shipping case.

In Amendment #35, Response to Question #3d, Bayer explained that the (b) (4) site is responsible for authorizing the release to market of the final market package. The criteria for releasing the final package for distribution include but are not limited to:

- Batch record review to ensure that all drug substance, drug product manufacturing, and final packaging processes were completed using approved procedures
- Ensuring drug product test results met specifications
- Ensuring all deviations are closed, and impacting change requests/validations are completed
- Facility and microbiological assessments are completed and acceptable.

SHIPPING STUDIES

Both the unlabeled drug product vials of Kovaltry and the final market packages (containing the lyophilized drug product, sWFI diluent, and administrative adapter) are shipped using temperature control systems designed to maintain their product integrity and temperature. The shipping temperature is (b) (4).

The shipping systems include (b) (4) contain a mechanical system to achieve temperature control (e.g., (b) (4) contain (b) (4).

The (b) (4)

In order to establish the suitability of the shipping process, shipping studies were performed which included physical and/or thermal testing. The purpose of the physical testing was to ensure that packaging design will adequately protect product from physical damage during shipment. The purpose of the thermal testing was to ensure that the temperature control system can maintain product temperature within an acceptable range throughout transport.

Physical Testing Results

Physical testing involved exposing the drug product packaging materials to (b) (4)

Testing was carried out with primary container closure and packaging components used for Kovaltry. Both vial cap types for Kovaltry, the reconstitution cap and the aluminum overseal were used in the transport study.

After exposure to the physical tests, the vials in the unlabeled drug product cases were visually inspected for defects (not more than (b) (4) rejection) and the caps were visually inspected as well (b) (4) rejection) and a (b) (4) test was performed with a criteria of (b) (4) pass. Both sets of tested vials, the vials with the reconstitution cap and the vials with the aluminum overseal, passed the visual inspection and (b) (4) test. Additionally, the market package cases were inspected for damage to the inside components and overall carton damage. The criteria for internal damage was (b) (4) rejects and all cases passed the testing meaning that the contents were adequately secured and packaged to provide for safe-handling from transport. The criterion for carton damage was no more than (b) (4) rejects and both configurations (one for the aluminum overseal and one for the reconstitution cap) passed the testing.

Thermal Testing

Thermal testing was performed to qualify the (b) (4)

Acceptance criteria were within the range established by stability studies for the product.

The shipping studies demonstrate the temperature control systems used to transport product provide adequate thermal control during transport.

Reviewer Comment: In order to perform an assessment of the shipping studies that were completed, DMPQ requested additional information regarding the number of units that were tested and the statistical relevancy of this size, copy of the thermal testing report in which the worst-case locations were determined, and a summary of the shipping procedure differences between Kogenate-FS and Kovaltry.

Information Request & Response (Amendment #35, Question #2): Regarding the shipping studies that you have performed on the unlabeled drug product vials of Kovaltry and on the final market packages, please address the following questions:

- a. Please identify the number of drug product vials that were included in the unlabeled drug product cases and in the market package cases that were exposed to the physical testing. Please explain why the number of units tested is representative of the typical drug product lot size.

Response: For the unlabeled drug product cases, (b) (4) aluminum seal cap vials (b) (4) cases of (b) (4) vials each), and (b) (4) reconstitution cap vials (b) (4) cases of (b) (4) vials each) were exposed to the physical testing. For the market package cases, (b) (4) drug product vials (b) (4) cases of (b) (4) market packages each, with one vial per market package) were tested. These numbers represent the maximum-load cases per configuration in (b) (4), and were chosen to correspond with the worst-case conditions within a shipment, rather than a product lot size.

- b. Please provide a copy of your final reports regarding the thermal testing to qualify the shippers and refrigerated trucks. Please explain your rationale for testing at the monitored sites and indicate how you determined the worst-case locations. Please clarify if the drug product units that were tested in the physical study were then tested in the thermal testing study.

Response: Bayer provided copies of the following reports regarding the thermal testing to qualify the (b) (4) which are utilized for US distribution:

- BV-000-PP-052 ISC (b) (4) *Shipping System Temperature Qualification*
Initial qualification of (b) (4), supports minimum payload
- BR-000-PV-023-03.01 *Qualification of the* (b) (4)
packed with (b) (4)
Additional qualification of (b) (4) to support increase of maximum payload
- PVR-PR-TC-0016.01 *Addendum to BR-000-PV-023-03.01: Qualification of the* (b) (4)
Addendum clarifying results from BR-000-PV-023-03.01
- BV-000-PV-021 *Shipping Validation for Packaged Kogenate-FS and* (b) (4)
(b) (4) *Custom Critical*
(b) (4) qualification

Bayer explained that the thermal testing monitoring locations within (b) (4) were chosen to assess the product temperature throughout the (b) (4) for minimum and maximum loads and hold and cold ambient temperatures. Within the minimum load, the monitoring locations were in contact with the product and at the top of the (b) (4), in order to monitor internal air temperature. Within the maximum load, the monitoring locations were adjacent to the product at (b) (4). As the (b) (4) is small in size (b) (4) the (b) (4) within the (b) (4) are symmetrically placed, and all Market Package cartons are identical, the monitoring locations were representative of the entire payload.

The thermal testing monitoring locations within the (b) (4) were at designated locations on the (b) (4) to obtain temperatures representative of the entire load. Worst-case locations were chosen as those with the most outside influence, such as (b) (4). The drug product units that were tested in the physical studies were not utilized within the thermal studies.

- c. Please identify any differences in the shipping procedures for Kovaltry than in the shipping procedures for Kogenate-FS.

Response: The existing Kogenate-FS shipping procedures will be utilized by Kovaltry, because both products have the same dimensions/thermal mass and use the same cold chain process.

Reviewer Comment: The results of the shipping validation indicate that the product will be maintained at the specified temperature during shipment and that the packaging is sufficient to prevent damage during transport.

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 Kovaltry is a water soluble (b) (4) protein and that it is recombinant replacement protein of the naturally occurring coagulation factor, Factor VIII. The protein is catabolized during human metabolism and no active molecule is excreted by the patient.

Information Request: Regarding your Categorical Exclusion Request for preparation of an Environmental Assessment, you are seeking the request in accordance with 21 CFR Part 25.31. In this Part, there are 10 sections (a through j) that identify which biological products are excluded and the reason. Your request does not specify which section of 21 CFR Part 25.31 you are seeking the exclusion. Please identify which specific section of 21 CFR Part 25.31 you are seeking the categorical exclusion request.

Response (Amendment #26, Question #17): Bayer clarified the categorical exclusion request is filed under 21 CFR Part 25.31 (c).

Reviewer Comment: Concur with the request for the Categorical Exclusion under 21 CFR 25.31 (c) as Bayer has explained that Kovaltry 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 approval of this application would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.