



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research**

TO: To file BLA STN 125577/0

FROM: Jie He, M.S., CSO, CBER/OCBQ/DMPQ/MRBII

THROUGH: Marion Michaelis, Chief, CBER/OCBQ/DMPQ/MRBII

CC: Cherie Ward-Peralta, RPM, CBER/OBRR/DBA/RPMB

APPLICANT: Baxter Healthcare Corporation [US. Lic#0140]

PRODUCT: BAX111- Recombinant von Willebrand Factor; Vonicog alfa [VONVENDI]

SUBJECT: Primary review memo

ADD: December 19, 2015

REVIEW RECOMMENDATIONS

I recommend additional information request

REVIEW SUMMARY

Baxter Healthcare Corporation (Baxter) submitted an original application under STN 125577/0 for the licensure of recombinant von Willebrand Factor (rVWF) for the prevention and treatment of bleeding episodes in adults (age 18 years and older) diagnosed with von Willebrand disease. The BLA was received by CBER on December 19, 2014. The manufacture of rVWF is performed in the existing Baxter establishments: (b) (4) Bulk Drug Substance (BDS) production; (b) (4) BDS production; and Thousand Oaks (California, USA) site for final drug product.

Recombinant VWF is planned to be marketed as a unit kit containing one vial of rVWF, one vial of sterile water for injection (sWFI) as diluent, and one Mix2Vial reconstitution device (which is 501(k) cleared). The Mix2Vial reconstitution device and the (b) (4) sWFI diluent have been previously approved and are currently in commercial use with other US licensed products for Baxter.

The rVWF is formulated as a sterile, nonpyrogenic, white or off-white, lyophilized powder preparation for intravenous injection and is stabilized with a mixture of sugars, salts, and amino acids. The rVWF final drug product (FDP) is supplied in single-dose glass vials, reconstitution with liquid diluent (sWFI), which is provided in a glass vial.

Pre-Licensing Inspections (PLI) were performed for the Baxter's (b) (4) facilities in (b) (4) from (b) (4) to support the review of STN 125577/0. A recommendation for waiver of PLI memo was signed by OBRR/DH and OCBQ/DMPQ on June 23, 2015 for Baxter's (b) (4),

(b) (4), Baxter's Thousands Oak, CA facility and the (b) (4)

As this is a recombinant product, this review was conducted under FDA's *Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-derived Product or a Monoclonal Antibody Product for In Vivo Use*. Under this guidance, limited information is required to be submitted regarding facility and equipment. As such, my review is based on this guidance document.

I. REVIEW NARRATIVE

Environmental Analysis (Categorical Exclusion)

Baxter requested categorical exclusion from environmental analysis for this BLA with respect to the manufacture of VONVENDI under 21 CFR 25.31(c), which provides environmental analysis exclusion for products containing substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Baxter stated that to their knowledge, no extraordinary circumstances exist under 21 CFR 25.15(d). VONVENDI is a protein based product that is composed of naturally occurring substances and void of any genetically modified organisms, is going to be used as a von Willebrand Factor replacement therapy in von Willebrand Disease patients. It is produced and formulated without the addition of any exogenous raw materials of human or animal origin in the cell culture, purification, or formulation of the final product. VONVENDI is formulated as a sterile, non-pyrogenic, white to off-white powder for intravenous injection. The product does not contain any preservatives and has tri-sodium citratedihydrate, glycine, mannitol, trehalose-dihydrate, and polysorbate 80 as stabilizers and excipients. None of the stabilizers and excipients present in VONVENDI have been found to be toxic or immunogenic.

Based on the information submitted and the nature of this product, I concluded that the sponsor's request for Categorical Exclusion from an Environmental Assessment under 21 CFR 25.31(c) is justified as this product is composed of naturally occurring substances and manufacturing of this product will not alter significantly the concentration and distribution of the natural substance, its metabolites, or degradation products in the environment, and no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

Items Reviewed

- STN 125577/0
- STN125577/0.10 Amendment in response to Information Requests of 5/22/2015 and 5/29/2015
- STN125577/0.12 Amendment in response to Information Requests of 7/30/2015

I reviewed the manufacturing processes of rVWF including the drug substance (DS) (b) (4) performed at Baxter's (b) (4) and at Baxter's (b) (4) and drug product (DP) (formulation, filling, and lyophilization) performed at Baxter's Thousand Oak California facility, as well as the manufacturing of the diluent performed at the contract manufacturer (b) (4)

My review focuses on the facilities, equipment, sterilization, lyophilization, container closure integrity testing, and the filling and packaging. The review is organized as the following sections:

- I. REVIEW NARRATIVE**
- II. DRUG SUBSTANCE**
- III. DRUG PRODUCT**
- IV. DILUENT**
- V. REVIEW QUESTIONS**

Facilities for rVWF Manufacturing

The following facilities in Table 1 are associated with the manufacture of rVWF DS, DP, and diluent. The testing sites are in Table 2.

Table 1: Facilities Associated with the Manufacturing of rVWF Drug Substance, Drug Product, and Diluent

Name and Address	Manufacturing Steps and/or Type of Testing	Last FDA Inspection
(b) (4)		
Baxter Healthcare Corporation 1700 Rancho Conejo Blvd. Thousand Oaks, CA 91320 FEI 1000519965 DUNS 009471603	(b) (4), formulation, filling, lyophilization, DP labeling and packaging VWF:Ag (b) (4); Bioburden (b) (4)	02/19-28/2014 Surveillance VAI
(b) (4)		

<div data-bbox="159 199 579 233" data-label="Text"><p>[REDACTED]</p></div>		(b) (4)
<div data-bbox="159 233 579 266" data-label="Text"><p>[REDACTED]</p></div>	<div data-bbox="579 233 1127 266" data-label="Text"><p>[REDACTED]</p></div>	<div data-bbox="1127 233 1408 266" data-label="Text"><p>[REDACTED]</p></div>

Table 2: Baxter's Testing Sites for (b) (4)

[illegible]

(b) (4)

Except the Baxter facility in (b) (4), all other facilities inspections were waived or were not subject to an inspection. Please refer to the inspection waiver memo of June 23, 2015 for details.

Product Description

Baxter Healthcare Corporation has developed the first rVWF bearing company code BAX111, INN name vonicog alfa, and the proposed proprietary name VONVENDI for the prevention and treatment of bleeding episodes in adults (aged 18 and older) diagnosed with von Willebrand Disease (VWD).

The rVWF is manufactured and formulated in the absence of animal or human plasma proteins. rVWF protein is expressed in Chinese Hamster Ovary (CHO) cells that also express the US licensed recombinant Factor VIII (rFVIII) product ADVATE. The isolated and purified rVWF FDP is supplied in single-dose glass vials (10 and 30 mL). The rVWF is for intravenous use after reconstitution with sWFI. It consists of a lyophilized powder for solution for injection, sterile water for reconstitution and Mix2Vial Device. The proposed nominal dosage strengths are 650 and 1300 IU/vial. One IU corresponds to the activity of VWF contained in one mL of healthy human plasma determined using a clotting assay. Each dosage strength is reconstituted using sWFI (5 and 10 mL) and swirled gently prior to intravenous injection.

Overview of Manufacturing

(b) (4)

26 Pages determined to be not releasable: b(4)

(b) (4)

3. FACILITIES

A. Heating, Ventilation, and Air Conditioning (HVAC) System

This facility, including Building (b) (4), has been previously inspected by FDA, but the areas used for rVWF manufacturing were not the focus of the previous inspections. Building (b) (4) site consists of (b) (4) the GMP production area for rVWF BDS is situated in the (b) (4) of Building (b) (4). The (b) (4) houses recombinant proteins manufacture and commonly used areas (b) (4) and equipment preparation, cold rooms, storage rooms, washing area with autoclave and washing machines). The technical supply system is located in the (b) (4), mainly the air handling units.

Potential product contamination from the manufacturing environment is minimized through the use of separate air handling systems, High Efficiency Particulate Air (HEPA) filters, and room air pressure differentials from critical to non-critical areas. The HVAC design criteria and method of operation are to provide and maintain temperature control, dehumidification, and room pressurization. Areas that require more stringent temperature control ((b) (4)) have dedicated mechanical systems separate from the HVAC system. EMPQ was conducted. The HVAC design and validation were reviewed during the PLI, and are covered in greater detail in the EIR.

Table 26: Description and Classification of Rooms in the GMP Production Area of Building (b) (4)

(b) (4)

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

(b) (4)

Gowning procedures are in place to protect both product and personnel. The ingress and egress of raw materials, equipment and personnel into the manufacturing area and process rooms are designed to control exposure of the product, and are described in SOPs. The facility is designed to minimize personnel traffic through the manufacturing rooms.

All direct product contact equipment are dedicated; some other equipment, such as buffer tanks, the washing machine and autoclave are shared equipment. Mix-up of the equipment of different products during cleaning/sanitization is prevented by applying measures defined in SOPs. The ingress and egress of equipment from different areas is also described in SOPs.

General Facility Cleaning

Established procedures are used to address the cleaning of manufacturing areas and equipment in accordance with frequencies established in SOPs. The disinfectants currently used at Baxter have been validated for effectiveness against in-house isolates that are most frequently detected in the production environment. The trending as well as the re-evaluation of the in-house flora is performed according to the respective procedures and intervals.

Production rooms are cleaned and disinfected according to specific written procedures as required by the designated room classification. Cleaning and disinfection of manufacturing floor, ceiling and walls is performed by qualified personnel, using appropriate cleaning aids and qualified disinfectant agents according to the existing SOPs for cleaning. Cleaning and disinfection of rooms is documented in cleaning log sheets for each room.

Reviewer's comments:

- *The facility cleaning was reviewed and discussed in more details during PLI and discussed in the EIR.*

Environmental Monitoring Program

Environmental monitoring was performed in all critical areas of the manufacturing facilities ((b) (4)) during the process performance qualification campaigns (campaigns (b) (4) (b) (4)

All environmental monitoring data collected was verified to be within the limits established in internal procedures.

Reviewer's comments:

- *The EM program was reviewed and discussed in more details during PLI and discussed in the EIR.*

4. EQUIPMENT VALIDATION

For all equipment, IQ and OQ have been performed and completed successfully. Major production equipment are listed in the Table 27 below:

Table 27: Major equipment and locations

Equipment	Validation Number	Room Location	Room Classification ^a	Manufacturing Step ^b	Equipment dedicated/shared
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(b) (4)

The IQ and OQ summaries and data are not provided in the submission, but firm stated in the BLA that these reports are all available upon request. Equipment qualifications were also reviewed during PLI, and discussed in EIR. Cleaning validations are discussed in section 5 below.

Autoclave

Autoclave (b) (4)

(b) (4)

Autoclave validation was covered in greater detail in PLI and discussed in EIR.

5. EQUIPMENT CLEANING AND CLEANING VALIDATION

(b) (4)

(b) (4)

Cleaning validation was performed for all direct-product contact surfaces and indirect-product contact surfaces. Worst case trace substances were used to soil the equipment (e.g. substances showing^{(b) (4)}

The sampling points were selected based on risk assessment regarding equipment design, accessibility and the cleaning process, and represent worst case areas for cleaning. Analytical tests such as (b) (4) were chosen to demonstrate sufficient removal of soil and cleaning agents. In addition, (b) (4) levels were measured to assess the microbiological status of the cleaned equipment.

Dirty Equipment Hold Time (DEHT) and Clean Equipment Hold Time (CEHT) were validated all based on three consecutive validation runs. The effectiveness of the validated cleaning procedures is regularly monitored by routine monitoring according to predefined and approved timetables and periodic revalidations.

Cleaning of Installed Equipment

Each type of equipment is cleaned with a defined sequence of cleaning steps dependent on the equipment design and the type of soiling. The last cleaning step of the cleaning program is (b) (4). All cleaning operations for the installed equipment are operated and controlled by the central computerized Process Control System (PCS).

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

(b) (4)

(b) (4)

FDA IR of July 30, 2015

FDA Question 1

(b) (4) acceptance limit for cleaning of skid (b) (4) is set at (b) (4) and actual data from all the process validation runs (b) (4) reported (b) (4). Please provide justification for the acceptance criteria and please also clarify if and what alarm limit has been established for this cleaning parameter.

Baxter Response

(b) (4)

(b) (4)

Reviewer's comments:

- The (b) (4) limits are in the acceptable range, but the (b) (4) /the cleaning acceptance criteria for (b) (4) are high compared to the results from cleaning validations. An IR was sent to the firm on August 18, 2015, and response is expected by September 2, 2015.

FDA IR of August 18, 2015

1. You stated that the acceptance criteria for (b) (4) samples during cleaning validation were defined individually for each type of equipment at (b) (4). However, the

reported acceptance criteria do not reflect the process capabilities as demonstrated by the results of the cleaning validation runs summarized in the table below. Please update your acceptance criteria to meet your process capabilities. Please justify your response.

(b) (4)

Reviewer's comments:

- *The firm has conducted cleaning validation for all the major equipment. Automatic cleaning and manual cleaning processes have been validated. Some of the cleaning acceptance criteria appear higher than their process capabilities. IR has been send to the firm requesting for justification and revisions to their acceptance criteria. Additional equipment cleaning was reviewed in greater detail during PLI and is further discussed in EIR.*

(b) (4)

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

(b) (4)

Reviewer’s comment:

- (b) (4) .

III. DRUG PRODUCT

The rVWF FDP consists of a lyophilized powder for solution for injection, sterile water for reconstitution and Mix2Vial Device. The proposed nominal dosage strengths are 650 and 1300 IU/vial. Each dosage strength is reconstituted using sWFI and mixed gently prior to intravenous injection.

Table 36: Drug Product Composition of VWF

Name of constituent	Unit and or percentage formula (for nominal dosage strengths)		Function	Reference to standards
	650 IU/vial	1300 IU/vial		
Recombinant Von Willebrand Factor	130 IU/mL	130 IU/mL	(b) (4)	(4)
Tri-Sodium CitrateDihydrate	15mM	15mM		
Mannitol	20g/L	20g/L		
Trehalose Dihydrate	10g/L	10g/L		
Glycine	15mM	15mM		
Polysorbate 80	0.1g/L	0.1g/L		

1. ESTABLISHMENT DESCRIPTION

Under U.S. License 140, the Baxter Thousand Oaks (TO) location includes existing licensed facilities for 1) the production of (b) (4), 2) the manufacture of final products, and 3) production support areas for the storage of materials/product, packaging of final products, and distribution. The (b) (4), formulation, filling, lyophilization, labeling and packaging operations for rVWF are performed at Building (b) (4) (Formulation and Filling Complex (b) (4)), Building (b) (4) (Plant service and QC labs) and Building (b) (4) (QC labs and office). (b) (4) includes (b) (4) fill lines, (b) (4) lyophilizers, (b) (4). Only Fill Line (b) (4) and (b) (4) are used for rVWF manufacturing, in addition to these other products: RECOMBINATE (BL 1013375/5289), HEMOFIL M (STN101448/5300), RIXUBIS (STN125446/0000), and other recombinant protein clinical products.

TO facility is a multiproduct facility, and refer to Table 35 for a list of the products manufactured at the TO facility.

Table 37: Thousand Oaks Facility Multi-Product Manufacture

(b) (4)	Product Type	Product Classification	Product Name	Product Status
	Biologic	Recombinant Protein	RECOMBINATE / Antihemophilic Factor (Recombinant)	Commercial (BL 103375)
	Biologics	Recombinant Protein	ADVATE / Antihemophilic Factor (Recombinant) Plasma /Albumin Free Method	Commercial (BL 125063)
	(b) (4)			
	Biologic	Plasma-Derived Protein	HEMOFIL M / Antihemophilic Factor (Human)	Commercial (BL 101448)
(b) (4)	Biologic	Recombinant Protein	RIXUBIS / Coagulation Factor IX (Recombinant) (rFIX)	Commercial (BL 125446)
	(b) (4)			

2. FACILITY

rVWF FDP is manufactured in TO Building (b) (4) using Filling Line (b) (4) includes controlled production areas for formulation, closure component preparation, sterile filtration, aseptic filling, product lyophilization, overcapping, and packaging operations. rVWF processing steps and locations are summarized in the table below:

Table 38: rVWF FDP Processing Steps and Locations

Production Step	Room	Operation
(b) (4)		
Sterile Filtration	(b) (4)	

Filling	(b) (4)
Lyophilization	
Transport of Lyophilized Product	
Capping	

A. Containment/Cross-Contamination

Product segregation and cross-contamination between products/materials are controlled via line clearance, area approval, cleaning, and labeling requirements per facility SOPs. Procedural segregation is performed through SOP TO-20-EN510.. The cleaning procedures are in place for the manufacturing production areas required for licensed product and development products manufactured at the Baxter TO facility.

To prevent product cross-contamination, area approvals are performed, per SOP TO-14-IA002 and SOP TO-14-IA009, either by means of physical or spatial separation. Those procedures included:

(b) (4)

The environment in the manufacturing areas is controlled and supported with an HVAC (system. Dedicated AHU supply processing areas, and maintain the pressure gradient that channels the air flow from critical to non-critical areas. In addition to maintaining air quality through the HVAC system, the firm stated that gowning procedures that are applicable to the process and environment are in place to protect both product and personnel. There are different gowning procedures in place for final bulk formulation, filling, aseptic process and packaging. Personnel are trained and enter manufacturing areas in a controlled manner by gowning per established written procedural requirements. Non shedding gowning material is used. The facility is designed to minimize personnel traffic throughout the manufacturing rooms.

The ingress and egress of raw materials, equipment and personnel relative to the manufacturing area and process rooms are designed to control exposure of the product. Line clearance and other SOPs are in

place to assure product segregation and the prevention of cross-contamination. Trained personnel using approved procedures perform facility cleaning. The cleanliness of the manufacturing environment is confirmed via the EM program defined in written procedures.

B. HVAC

The Formulation and Filling facility is comprised of areas with room classifications ranging from ISO Class (b) (4) to unclassified areas. The air flow and pressure differentials for the area employ a cascade effect that results in air flow progressing from manufacturing areas, outward to areas designated to have less stringent requirements. The HVAC of the formulation and filling manufacturing areas are qualified and include the following routine testing:

- HEPA Certification
- Airflow Visualization
- EM
- HVAC Recovery Testing (b) (4)
- Media Fills

The area is routinely cleaned per SOP TO-09-JE501, *Sanitization and Cleaning of Aseptic Filling, Sterility Test Rooms, Final Container Drying, and Preparation Production Rooms*. Furthermore, the facility is routinely monitored per SOP TO-12-LG510, *Environmental Monitoring Program for Bulk Formulation Area, Preparations Area, Aseptic Fill Complex, Sterility Suite and Water Test Area*. HEPA's are recertified on a routine basis to ensure the validated state is maintained per SOP TO-20-EL700, *Certification and Recertification of HEPA Filters*.

The firm provided monitoring results, HEPA certification results, and EM results for rVWF manufacturing areas. In addition, smoke study for at-rest and in-operation for (b) (4) was successfully completed in December 6, 2013 per SOP TO-20-EB700. Firm also stated that smoke study is performed on a routine basis.

C. Environmental Monitoring

The firm provided EM sampling locations for equipment and rooms used for rVWF DP manufacturing. (b) (4) of consecutive EM were performed following the latest Formulation and Filling facility shutdown and startup activities. All at-rest EM test results for all rooms within the Formulation and Filling facility met the criteria specified in SOP TO-12-LG510, for the appropriate room classification. EM is continuously being performed on a routine basis. The firm provided EM data for at-rest and in-operation for the rVWF manufacturing areas in 3.2.A.1. The sampling locations and frequencies were reviewed and seem adequate. Process simulation runs using both 10 mL and 30 mL vials were conducted successfully, under Protocols TO-29-7016-G, TO-29-7016G002 and TO-29-7016G003 to demonstrate the (b) (4) can be operated in a manner consistent with the requirements and specifications for routine operations. The EM results during media fill are summarized in the media fill section below. For routine operations, the EM monitoring and acceptance criteria and test results for formulation and filling facility are summarized in the table below:

Table 39: Environmental Monitoring, Action Limits, In-Operations

(b) (4)

(b) (4)

Reviewer's comments:

- *The EM acceptance criteria and results indicated the EM program is effective.*

Media Fill

(b) (4)

1 Page determined to be not releasable: b(4)

(b) (4)

During the manufacture of the process simulation runs, non-conformances were recorded. A total of nine events were initiated and assessed for the overall severity level and occurrence rate for probability. Root cause studies were conducted, corrective actions were taken, and product impacts were analyzed. These were deemed have no impact to the product. The EM was representative of manufacturing operation conditions. All monitoring was within limit with the exception of one out-of-limit result in room (b) (4) during media fill (b) (4) and samples being exposed longer than the specified exposure limit during media fill (b) (4).

D. Water for Injection (WFI)

The WFI system is currently approved for the manufacture of licensed TO products. The WFI system consists of a (b) (4) to the manufacturing areas, and (b) (4) The WFI system is designed to provide water to WFI use-points on the distribution loop, including the (b) (4)

Table 43: WFI Requirement

(b) (4)

(b) (4)

(b) (4)

3. MANUFACTURING PROCESS FOR DP

(b) (4) Baxter TO facility for further manufacturing into FDP. The manufacturing processes included (b) (4), formulation, filling, lyophilization, capping, (b) (4) testing, visual inspection, packaging and labeling are performed. An overview of the manufacturing process is outlined below:

Figure 12: Overview of rVWF FDP Manufacturing Process

(b) (4)

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

(b) (4)

FDA IR of May 22, 2015 Question 2d

Please confirm that the lyophilization cycle is fixed. Please provide detailed information on any changes made for any of the validation runs.

Baxter Response

Baxter confirms that the lyophilization cycle is fixed and controlled via a recipe specific for rVWF. No changes were made to the fixed lyophilization cycle for any of the validation runs.

FDA IR of May 22, 2015 Question 2e

Please clarify if fixed shelf locations will be used for both minimum and maximum loads in (b) (4) for your routine manufacturing process.

Baxter Response

Baxter clarifies that fixed shelf locations will be used for both minimum and maximum loads into (b) (4) for routine manufacturing process. For a minimum load, only shelves (b) (4) are used when loading rVWF product, whereas for a maximum load, only shelves (b) (4) are used for loading rVWF product.

Reviewer's comments:

- Firm confirmed that the production lyophilization process uses fixed cycle parameters, and fixed shelf locations are used in production for all loads .*

G. Unloading of Lyophilized Vials: (b) (4)

H. Capping and Laser Coding: (b) (4)

- I. Labeling and Packaging:** Labeling and packaging of manufactured lots of the final dosage form is performed in designated areas using vial labeler and unit carton labeler. The vials are packaged under ambient conditions. During the packaging operation the temperature of the vials must not exceed +30°C.

In-Process Controls and Testing for DP

(b) (4)

- (b) (4)

Summary of all in-process control and testing are listed in the table below:

Table 44: In-Process Control and Testing

(b) (4)

Release and Stability Specifications

The release specifications and stability specifications for DP are included in the submission. The Table 43 below summarizes the specifications that are under DMPQ's purview.

Table 45: Release and Stability Specifications for rVWF FDP

Parameter	Test Method	Acceptance Criteria
Sterility	(b) (4)	Sterile
Endotoxin	(b) (4)	(b) (4)
Appearance (lyophilized cake)	(b) (4)	White to off-white friable powder
Appearance (reconstituted solution)	(b) (4)	Clear, colorless solution, free from particles
Reconstitution Time	(b) (4)	(b) (4)
Residual Moisture	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Particulate Matters	(b) (4)	(b) (4)

The proposed shelf life for rVWF is 36 months at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. Formal stability studies are being conducted to assess the stability of the rVWF lyophilized DP representing both dosage strengths (650 IU and 1300 IU) all manufactured using commercial-scale rVWF DS, produced in Baxter's (b) (4) facility (b) (4). The conditions defined in the stability studies have been chosen to provide a stability assessment at the routine storage temperature ($+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$), room temperature ($+30^{\circ}\text{C}$ (b) (4)) as well as under accelerated (b) (4) storage conditions. A temperature excursion study is being performed by simulating the excursion to $+30^{\circ}\text{C}$ for up to (b) (4) after storage at $+5^{\circ}\text{C}$ for 18 months. Furthermore, in-use stability is evaluated by performing reconstitution studies. A total of (b) (4) lots of FDP (clinical lots and conformance lots) are on long term stability studies. All stability specifications including sterility (Sterile), endotoxin (b) (4) and other physical characterizations (appearance, reconstitution time, moisture and particulate matters) were met that were under DMPQ's purview.

All of the specifications for FDP can be found in Section 1 of eCTD 2.3.P - Drug Product [Control of Drug Product]

4. PROCESS VALIDATION for DP

For process validation the firm completed process consistency, media fill, sterile filter, and hold time validations.

A. PROCESS CONSISTENCY VALIDATION

Validation and evaluation studies were performed to demonstrate manufacturing process control, robustness and consistency. The process validation design is shown in Table 46.

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

(b) (4)

FDA IR of May 22, 2015 Question 2d

Please confirm that the lyophilization cycle is fixed. Please provide detailed information on any changes made for any of the validation runs.

Baxter Response

Baxter confirms that the lyophilization cycle is fixed and controlled via a recipe specific for rVWF. No changes were made to the fixed lyophilization cycle for any of the validation runs.

FDA IR of May 22, 2015 Question 2e

Please clarify if fixed shelf locations will be used for both minimum and maximum loads in (b) (4) for your routine manufacturing process.

Baxter Response

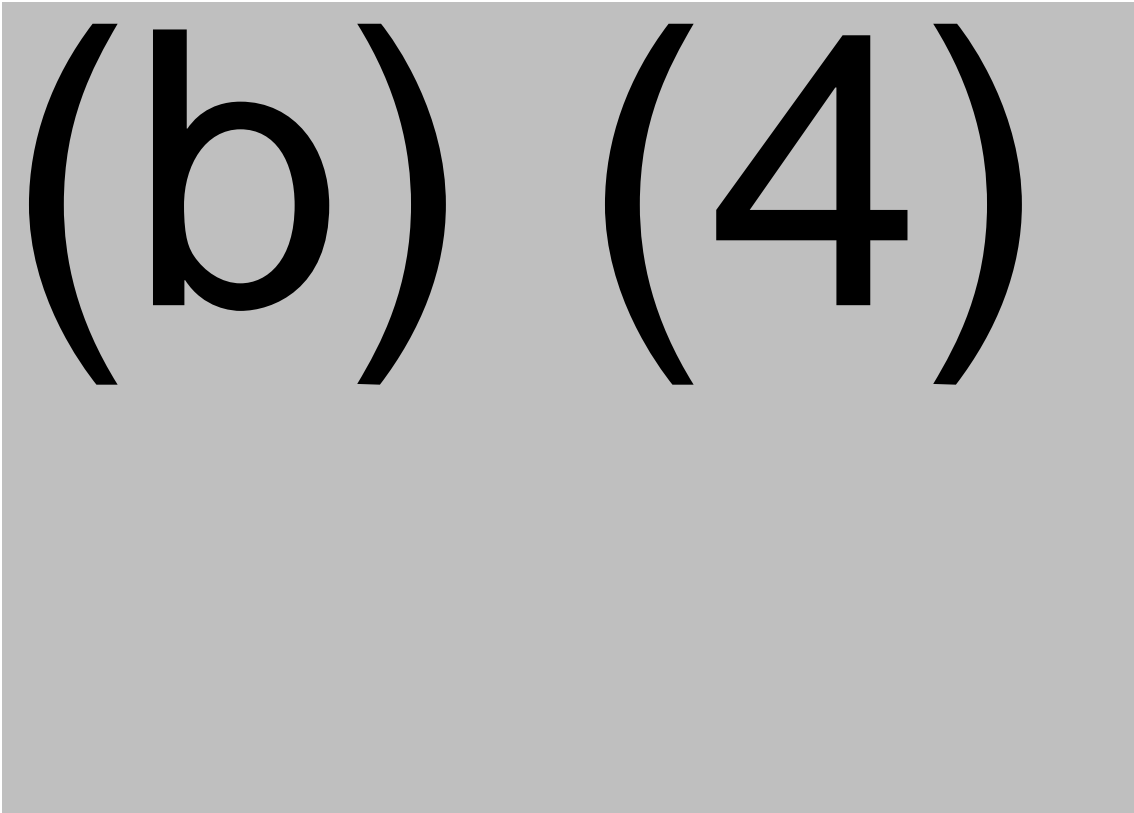


Baxter clarifies that fixed shelf locations will be used for both minimum and maximum loads into (b) (4) for routine manufacturing process. For a minimum load, (b) (4) are used when loading rVWF product, whereas for a maximum load, (b) (4) are used for loading rVWF product.

Reviewer's comments:

- *Firm confirmed that the production lyophilization process uses fixed cycle parameters, and fixed shelf locations are used in production for all loads.*

B. LYOPHILIZER PRODUCT TEMPERATURE MAPPING

Product Temperature Mapping was performed per Protocols for both the 10 mL and the 30 mL vials. A maximum load was processed in lyophilizer (b) (4) for each vial and stopper combination (i.e. 10 mL vials with 20 mm rubber stoppers and 30 mL vials with 20 mm rubber stoppers). (b) (4)



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

(b) (4)

Cake Appearance

There was no unusual cake structure observed for all (b) (4) rVWF product vials for the 10 mL vials and (b) (4) rVWF product vials for the 30 mL attached with temperature probes.

Reviewer's comments:

- *The results from this validation demonstrate that the rVWF product temperature profile was acceptable for both vial types. The data have shown the fixed lyophilization cycle is sufficient to maintain product temperature below collapse temperature during the entire primary drying phase even at the worst locations, and the primary phase also has sufficient time at the end of the phase to ensure completion of primary drying before moving into next phase. The product temperature variations are low, demonstrating the process is tightly controlled.*

C. PROCESS VALIDATION WITH CONFORMANCE LOTS

The manufacture of conformance lots was performed per Protocol TO-67-0776P008, and (b) (4) consecutive lots of rVWF were produced ensuring (b) (4) successful conformance lots at both potencies. For each dosage strength, a minimum load, a mid-sized load and a maximum load were used for validations.

(b) (4)

All process parameters for all the lots tested were within the specified limits, demonstrating that the process parameters were reproducibly controlled for the pharmaceutical preparation processing step.

(b) (4)

(b) (4)

Deviations occurred during conformance lots were discussed in the submission, and they appeared to have no product impact, but I defer the review of them to product office. The firm provided critical and major manufacturing deviations during process validation in section 3.4 of eCTD 3.2.P.3.5 – Drug Product – Process Validation. They include material defects, operator error and protocol generation error, and equipment failure, the firm conducted investigations on all of them and provided resolutions. I reviewed those under DMPQ purview and I agree that there were no impact to the product or to the process validation studies.

VISUAL INSPECTION

Visual inspection is performed manually on 100% of unlabeled final container vials per SOP by qualified inspectors. All inspectors are trained and qualified per the requirements of TO-14-HB001. The

inspection procedures and conditions are defined in SOP. A qualified product inspector will review questionable unlabeled final containers to ensure that defects and defect sizes are under the reject size as per Form TO-99-00506. Vials identified as acceptable shall be verified by QA Inspector prior to adding them back to the manufacturing process. A defect classification table is listed below:

Table 50: Defect Classification

(b) (4)

OTHER MAJOR EQUIPMENT/SYSTEMS FOR DP

Each piece of equipment was evaluated to determine the extent of validation required to accommodate rVWF manufacture. Several pieces of major equipment were previously validated for the manufacture of RECOMBINATE, HEMOFIL M and/or RIXUBIS and did not require any further validation to

accommodate the manufacture of rVWF, because the protein content in rVWF is much less than the other approved product and not considered as worst case in terms of the cleaning process. For autoclave, new validation has been conducted with the load patterns used for rVWF manufacturing, and reviewed in more details below.

(b) (4)

(b) (4)

5 Pages determined to be not releasable: b(4)

(b) (4)

EQUIPMENT CLEANING

Baxter stated that rVWF is not considered the worst-case soil from a cleaning perspective since the protein concentration of rVWF is much lower than their currently approved products (RECOMBINATE, HEMOFIL M and/or RIXUBIS). So for some product contact equipment, the previous cleaning validations have been used, and after each cleaning in production, the (b) (4) are tested to ensure the process is under control and effective.

1. Non-Product Contact Surfaces And Equipment

Cleaning/disinfection of non-product contact surfaces and equipment are performed by (b) (4)

The cleaning is documented in Form TO-99-00224, Equipment Clean and Use Log per SOP TO-20-EA019, Equipment Clean and Use Log Documentation for Manufacturing.

2. Small Parts Cleaning

Prior to production use, small parts (filter housings, (b) (4), gaskets, stainless steel fittings, valves, and other auxiliary non-product contact small parts) are cleaned with (b) (4) and then (b) (4)

The cleaning procedure was validated under Protocol TO-67-0652R. Post-Cleaning Test Specifications are summarized in the Table 54 below:

(b) (4)

(b) (4)

CONTAINER CLOSURE FOR DP

Description of the container closure systems used for the rVWF FDP is provided in Table 56.

Construction materials of each primary packaging component are listed in Table 57. The specifications for each component are referenced in Table 56.

Table 56: Description of Drug Product Container Closure System

Strength	Fill Size	Container Size(s)	Description
650 IU VWF:RCo/vial	5 mL	10 mL	(b) (4) Glass Vial (b) (4) 20mm (b) (4) rubber (b) (4) (b) (4) stopper Aluminum crimp cap (b) (4) (b) (4)
1300 IU VWF:RCo/vial	10 mL	30 mL	(b) (4) Glass Vial 30 mL 20mm (b) (4) rubber (b) (4) (b) (4) stopper Aluminum crimp cap (b) (4) (b) (4)

Table 57: Materials of Construction of Each Primary Packaging Component

Package Component	Materials of Construction	Manufacturer
Glass Vial (650 IU VWF:RCo /vial)	(b) (4)	(4)
Glass Vial (1300 IU VWF:RCo /vial)		
Stopper		
Crimp cap		

Table 58: Specifications of Each Primary and Functional Secondary Packaging Components

Packaging Component	Specification
Glass Vial (650 IU VWF:RCo/vial)	(b) (4) (4)
Glass Vial (1300 IU VWF:RCo/vial)	
Stopper	
Crimp cap	

The containers comply with the requirements for neutral glass, (b) (4) as described in current (b) (4) (b) (4). The containers also meet the requirements for (b) (4) glass per the current (b) (4). The stoppers meet the

chemical requirements of the current (b) (4)

and the requirements of the current

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

The 30 mL glass vials were initially manufactured by (b) (4)

. An IR was sent to the firm on May 22, 2015 as the following:

FDA Question 2c

Please clarify if validation studies were performed using all vials from the qualified vendor. If not, please justify why this is acceptable. Please provide detailed side by side specification comparison sheet for the 30 mL vials used in the validation and in routine production.

Response

Validation studies were performed using the 10 mL vials from (b) (4) and the 30 mL vials from (b) (4). Both vendors are qualified suppliers for Baxter. These vials were used for the Phase III clinical lots and the process qualification lots.

The 30 mL glass vials used for the Phase III clinical lots and the process qualification lots, manufactured by (b) (4) were manufactured according to (b) (4) line quality level. (b) (4) line provides inline dimensional control but no cosmetic inspection of the glass during the manufacturing process. However, after completion of the process qualification lots, the manufacturer of the 30 mL vials ((b) (4)) was required to make a manufacturing line change to a newer line inside the same manufacturing facility. This newer manufacturing line, referred to as (b) (4), has the capability to perform on-line camera inspection for glass defects, which increased the quality level of the vials resulting in tighter acceptance criteria for visual glass defects in the specification document.

A new internal part number for the 30 mL vial was created (b) (4) to reflect the higher visual inspection quality level. The higher quality level glass was made with the same glass (b) (4) using the same tools, and in the same (b) (4) manufacturing facility as the (b) (4) line quality glass. The vial with this new part number is now used in routine production but is dimensionally identical to the (b) (4) vial, as illustrated in the Table 3 and Figure 7 below. Since there was no impact from the manufacturing line change (same manufacturing process, materials, and dimensions), the higher visual inspection quality level of the 30 mL vial and the new internal part number do not therefore impact the previously executed validation studies.

(b) (4)

Reviewer's comments:

- The higher quality level glass was made with the same glass^{(b) (4)}, using the same tools, and in the same (b) (4) manufacturing facility as the (b) (4) line quality glass. The only difference is the new cosmetic inspection camera used in the vial production line for (b) (4), and both vials have identical specifications on all measurement. I consider the (b) (4) vials are acceptable to be used in DP production.

The stoppers meet the chemical requirements of the current (b) (4) and the requirements of the current (b) (4).

Container Closure Integrity for DP

CCIT for the 10 mL and 30 mL vials were done with (b) (4) tests as provided in CCI qualification reports TO-64-0787Z001 (for 30 mL vials) and TO-61-0696Z (10 mL) in amendment 10 with results to show the FDP vials and stoppers were qualified using (b) (4) test. The container closure system for the 10 mL and 30 mL vials are summarized in the tables below:

(b) (4)

Reviewer's comments:

- The (b) (4) test results and the long term stability data all support the qualification of the vials. The FDP vials are also undergoes a (b) (4) test for (b) (4). Together, this provided confidence that the container closure systems have been qualified and under control.

MIX2VIAL, (b) (4) for Reconstitution of rVWF Final Drug Product

The Mix2Vial line of Transfer Devices was developed for the purpose of allowing quick transfer of diluent into vacuum powder vials and aspiration of ready drug into a syringe after detachment. The Mix2Vial is composed of two vial adapters, one with a female luer and the other with a male lock. These two components are pre-assembled at the factory.

The family of Mix2Vial devices are 510(k) cleared [510(k) # K031861] and CE marked. They are distributed by MEDIMOP Medical Products Ltd., a West Company. A schematic of the device can be found in Figure 14.

(b) (4)

Labeling and Packaging

Each lot of rVWF DP with the nominal potency of 650 IU and 1300 IU is packaged into a product kit consisting of one product vial, one diluent vial containing approximately 5 mL or 10 mL of SWFI (5 mL SWFI is used to reconstitute 650 IU/vial, whereas 10 mL SWFI is used to reconstitute 1300 IU/vial), one Mix2vial Transfer Device, and one package insert (PI). The unit carton is constructed of (b) (4)

(b) (4)
(b) (4) width for the 650 IU configuration and (b) (4)
width for the 1300 IU configuration.

Shipping of FDP

The US domestic standard shipping packaging configurations for both dosages of rVWF were conducted using vibration and shock tests according validation protocol. The standard packaging was qualified without any defect.

The firm stated that the domestic shipping is following the existing shipping method per SOP TO-16-CB506 “*Shipping of final product and intermediates (Domestic)*”. Simulated shipping validation has been performed by (b) (4). The test settings used were as follows:

(b) (4)

(b) (4)

Vibration and shock (drop) tests were conducted. The Results showed no visible physical damage (cracks or breaks) to the product vial or sWFI vial (0 failures per case of (b) (4) kits) for both the 650 IU and 1300 IU configurations. Simulated shipping study of the rVWF US shipping configurations have been successfully completed with no damage (0 defects per case) to product vials or SWFI vials after shock, vibration, and compression testing per (b) (4).

The firm stated in the BLA that qualification of the shipping from Baxter’s TO facility to (b) (4) will be performed under protocol PR-68-14024, 2 to 8°C

Temperature controlled product distribution Process Qualification between Baxter Thousand Oaks to (b) (4) using routine production lots of rVWF and other Baxter Thousand Oaks Products.

Reviewer's comments:

- The firm was asked to provide an update about FDP shipping study.

IV. sWFI DILUENT

The rVWF diluent is an aseptically filled, (b) (4) sWFI and used for reconstitution of 650 IU/vial and 1300IU/vial lyophilized DP, which are supplied in 5 mL and 10 mL glass vials respectively. The sWFI diluents are manufactured by (b) (4). The identical sWFI products, (b) (4) sWFI have previously approved for the following Baxter products: (b) (4). Since these identical sWFI diluents have been previously approved in the other BLA as summarized in the Table 63, review of the sWFI diluents in this memo is limited to providing the specifications and overview of the manufacturing.

Table 63: Summary of Baxter's US Licensed Products Co-Packaged with 5mL and 10mL SWFI Manufactured by (b) (4)



Table 64: Compositions for sWFI

Ingredients	Unit Formula (per vial)	Function	Reference to Standards
Water for injection 6mL vial	(b) (4)	(b) (4)	(b) (4)
Water for injection 10 mL vial	(b) (4)	(b) (4)	(b) (4)

Table 65: sWFI container closure systems

6 mL Container	6 mL vial, (b) (4) glass
Closure	20 mm, (b) (4) rubber with (b) (4)
Crimp Cap	20 mm, Flip-Off Cap, aluminum, Grey
10 mL Container	10 mL vial, (b) (4) glass
Closure	20 mm, (b) (4) rubber stoppers, (b) (4)
Crimp Cap	20 mm, Flip-Off Cap, aluminum, Light Blue

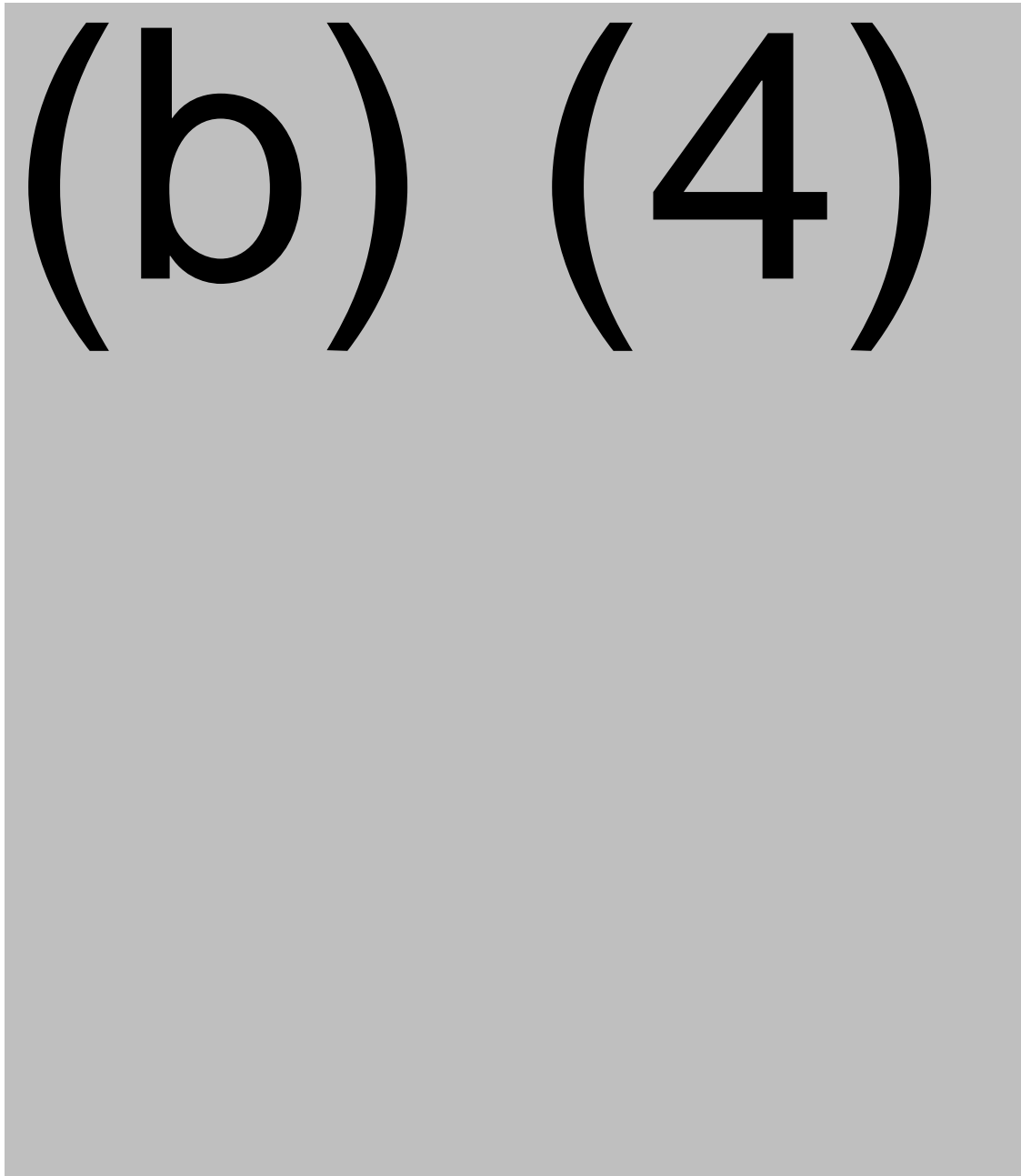
Establishment Description

sWFI (5 mL, 10 mL) is manufactured by contract manufacturer (b) (4) is also the sWFI diluent supplier for Baxter other FDA approved product using the same 5 mL and 10 mL vials as discussed earlier.

Diluent Manufacturing Process and Process Control

sWFI is prepared from WFI in bulk. After filling in final vials, (b) (4) and passed on to QC. The process flow is listed in the Figure 16 below:

Figure 15: Method of Manufacture Flow Sheet- sWFI



EQUIPMENT PREPARATION - Filtration equipment, vessels, filling equipment and other equipment are cleaned and sterilized.

COMPOUNDING

The (b) (4)

In-process controls:

(b) (4)

FILTRATION

(b) (4)

FILLING

Container: neutral glass vials, (b) (4) complying with (b) (4), Rubber stoppers: (b) (4) rubber stoppers (b) (4). The vials are filled (b) (4) in a class (b) (4) area.

AUTOCLAVING

(b) (4)

(b) (4)

VISUAL INSPECTION

The vials are 100 % inspected for particles and liquid level using a fully automated inspection machine. The visual inspection is performed with a fully automatic visual inspection machine working with a camera system. The inspection program was validated with a product specific test set. The program is designed to inspect the vial for cap defects, particle defects in product solution, presence of product solution and damage on the vial.

LABELING AND PACKAGING

Labeling and packaging is performed at Baxter Healthcare Corporation, Thousand Oaks, California according to current GMP requirements. Prior to starting the labeling and packaging operations, the identification of the product is assured by comparing the label on the containers holding the unlabeled product with the packaging release documentation provided by QA. The labeling and packaging materials are issued, verified and the lot specific data are imprinted and 100% verified. All components used are controlled to be in accordance with the packaging order. During the packaging operation, identity tests are carried out on the labeled and packaged final product according to a statistical sampling plan. The final units are packed in cartons, sealed and labeled with product name, lot number and number of product units enclosed.

PROCESS VALIDATION FOR DILUENT

Firm is the approved sWFI diluent supplier for other FDA approved product. Firm provided a tabular comparison for the 5 mL and 10 mL sWFI to all these products:

(b) (4)

Reviewer's comments:

- *The two types of vials are identical to those already been approved sWFI vials for other US products.*

(b) (4)

1 Page determined to be not releasable: b(4)

(b) (4)

Stability

Stability study up to (b) (4) at +5°C are provided and all met specifications.

Media Fills

Since the diluent is (b) (4), media fill study is not required.

Container Closure System for Diluent

The firm submitted CCIT validation reports done in 2008 on the same vials previously submitted with other BLAs. (b) (4)

Extractable and leachable

Study reports for extractable and leachable for vials and stoppers were provided, and review of the report is deferred to product office.

Facility and Equipment for Diluent Manufacturing

(b) (4)

Reviewer's comments:

- *The submission does not contain facility and other equipment information. Considering the firm is currently approved for providing identical 5 mL and 10 mL sWFI diluent vials for (b) (4) other FDA approved products to Baxter, and firm uses the same equipment and facility to manufacturing these identical diluent, I consider it is not necessary to request additional information on facility and the equipment.*

FDA IR of August 19, 2015

FDA Question 1

1. You stated that the acceptance criteria for (b) (4) of the final (b) (4) samples during cleaning validation were defined individually for each type of equipment at (b) (4). However, the reported acceptance criteria do not reflect the process capabilities as demonstrated by the results of the cleaning validation runs summarized in the table below. Please update your acceptance criteria to meet your process capabilities. Please justify your response.

(b) (4)

(b) (4)

FDA IR of August 27, 2015

1. Regarding cleaning validation at Thousand Oaks facility:

- You provided the acceptance criteria for your cleaning validation for equipment and small parts used for FDP manufacturing process (including items used for fill and finish processes, such as (b) (4), etc.) as listed in the table below. You also provided data collected during the cleaning validation of some of the equipment except for the small parts. However, the current (b) (4) acceptance criterion does not reflect the process capabilities demonstrated by the available results from the cleaning validation runs. Please update your acceptance criteria for (b) (4) to meet your process capabilities. Please justify your response.
- Please provide justifications on why (b) (4) is not part of the acceptance criteria

(b) (4)

2. Regarding (b) (4) :

- Please clarify if (b) (4) are dedicated to rVWF or shared with other products
- Please provide the cleaning validation data for (b) (4)

Reviewer's comment:

- *Pending IR responses are reviewed in the addendum review memo.*