



MEMORANDUM

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

To: File of BLA 1255577 & Cherie Ward-Peralta, RPM
From: Chava Kimchi-Sarfaty, CMC reviewer, Laboratory of Hemostasis, DHRR/OBRR
Through: Mark Weinstein, Associate Deputy Director, OBRR
Timothy Lee, Acting Chief, LH /DHRR/OBRR
Subject: Final review of CMC information in BLA 1255577 for VONVENDI, von Willebrand Factor (previously BAX111) for the prevention and treatment of bleeding episodes in adults (age 18 and older) diagnosed with von Willebrand disease

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I Background

This memorandum summarizes the review of the CMC information in Baxter’s BLA 1255577 to evaluate the safety and efficacy of VONVENDI, von Willebrand Factor (Recombinant rVWF), for the treatment of bleeding episodes in adults (age 18 and older) diagnosed with von Willebrand disease (VWD).

Human von Willebrand Factor (VWF) is a blood glycoprotein that is initially synthesized as a 2813 amino acid pro-VWF molecule. The pre-pro-VWF is composed of a 22 amino acid signal peptide, a 741 amino acid pro-peptide and a 2050 amino acid mature VWF subunit. The pro-VWF is composed of four repeats (A-D), which contain functional domains that have been identified as interaction sites with Factor VIII (FVIII), platelet glycoproteins GPIb and GPIIb/IIIa, collagen and heparin.

VWF has multiple post-translational modifications; it is composed of a series of high molecular multimers that range between approximately 500 kDa (VWF dimer) to >20,000 kDa. The monomer of VWF has an apparent molecular weight (by SDS-PAGE analysis) between 250 and 270 kDa. It dimerizes via a C-terminal disulfide bond and further N-terminal multimerization of VWF dimers results in the characteristic multimers of the VWF protein. In the secreted protein, all cysteine residues, which are abundant in all of the domains except for the triplicated A-domains, appear to be paired with disulfide bonds. The mature subunit is extensively glycosylated; 19% of the VWF mass are carbohydrates (10 O-glycans, which are predominately found in the A-repeat, and 12 N-glycans, which are distributed over all domains of the molecule). One or both of the oligosaccharides at Asn384 and Asn468 of the mature subunit are sulfated.

ABO-blood type antigens are found on 15% of the N-glycans in VWF circulating in plasma. The rVWF, and the VWF that is stored in platelets do not contain ABO blood type antigens.

This product will correct the hemostatic abnormalities in VWD patients by: (a) establishing platelet adhesion to the vascular subendothelium at the site of vascular damage and (b) correcting the associated functional FVIII deficiency by binding to endogenous FVIII (which is produced normally by VWD patients) and stabilizing this factor.

The following replacement therapies, which were originally developed for the treatment of hemophilia A, are currently available for patients with VWD: (i) plasma FVIII concentrates that also contain VWF and (ii) purified VWF derived from human plasma,.

The applicant (Baxter Healthcare Corporation) has developed VONVENDI, a recombinant human VWF (rVWF) protein. The rVWF is manufactured and formulated in the absence of animal or human plasma proteins. Recombinant VWF protein is expressed in Chinese Hamster Ovary (CHO) cells that also express

the licensed rFVIII product ADVATE. (b) (4) by recombinant furin, and (b) (4). Recombinant VWF is formulated as a lyophilized powder for intravenous infusion, after reconstitution with sterile water for injection. The proposed nominal dosage strengths are 650, and 1300 IU/vial.

II Scope of the review

The CMC review of the BLA for VONVENDI is shared with Zuben Sauna. This review addresses the following CMC product topics; all other CMC topics were reviewed by Zuben Sauna:

(b) (4) Drug product (DP)

- Description of the manufacturing process and its control
- Starting materials
- Physicochemical characterization
- *In vitro* biological activity
- Impurities and clearance of process-related impurities
- Justification for the proposed release specification
- Conformance batch manufacture
- Excipients and their control
- Product diluent
- Container closure description and control
- Analytical procedures and reference standards
- Stability
- Safety of adventitious agents

Shipment validation studies were reviewed by the Division of Manufacturing and Product Quality (DMPQ) (Jie He) with the exception of the shipping validation studies for rFurin. IR was sent to Baxter regarding these validation studies.

Baxter has provided an acceptable data package, which has adequately demonstrated the establishment of a commercial manufacturing process, validated to consistently produce rVWF that meets specified criteria for quality attributes that are linked to product quality, safety and efficacy. Process design and development integrated comprehensive product characterization, process characterization studies and quality risk assessment tools to establish appropriate process parameter control ranges and quality attribute specified ranges.

I found the CMC information, which I reviewed, to be adequate and complete.

III Review

Preparation of stable cell lines carrying the (b) (4) rVWF

Manufacturing sites

Table 1 is copied from section 3.2.S.2.1 and lists all the BDS manufacturing sites:

(b) (4)

The (b) (4) formulation, filling, lyophilization, labeling and packaging operations are performed at Baxter Healthcare Corporation, 1700 Rancho Conejo Blvd. Thousand Oaks, CA 91320 USA.

(b) (4)

Human recombinant VWF

(b) (4)

Cell culture

(b) (4)

(b) (4)

(b) (4)

[Redacted]

Reviewer's comment:

The description of the preparation of the stable cell line is adequate and the genetic stability results are satisfactory.

Description of manufacturing process, process controls and starting materials

- (b) (4)
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

(b) (4)

The validation studies of each step and the process changes that were implemented during the life-cycle of the IND are discussed in Zuben Sauna's review.

Reviewer's comment:

The rVWF purification process is adequate.

The following Chemistry, Manufacturing and Controls product issues were discussed and resolved with Baxter during the review of the IND:

1. *Establish similar kinetics of ADAMTS13 degradation to plasma-derived VWF (pVWF).* Baxter did not provide data that could demonstrate that rVWF multimers show the same pattern as plasma-derived VWF (pVWF). Consequently the Agency placed a clinical hold in May 2008 and requested that Baxter demonstrate that rVWF show the same sensitivity to ADAMTS13 cleavage as pVWF. In addition Baxter was requested to perform studies that could show a correlation between the changes in multimeric structure of the VWF molecules over time after ADAMTS13 cleavage to changes in VWF activity using VWF:RCo and/or VWF:CB the ADAMTS13 cleavage. Baxter performed additional studies and submitted data that adequately compares the kinetics of ADAMTS13 degradation of the rVWF to that of pVWF. Additionally, Baxter correlated the changes in multimeric structure of the VWF molecules over time to changes in VWF activity, such as VWF:RCo and/or VWF:CB.
2. *Establishment of test to detect host cell proteins derived from the (b) (4).* Baxter addressed the Agency's request to detect and evaluate the HCP impurities, including those from (b) (4). Baxter added a (b) (4) analysis to compare the amount of host cell derived proteins from the (b) (4). The results of the test are satisfactory.

(b) (4)

(b) (4)

5. *Establishment of (b) (4) to clear sub-visible insoluble particles and test method for drug product appearance.* Data from stability studies conducted by Baxter showed the presence of sub-visible insoluble particles in the final drug product which appear only with vigorous shaking of the product. These particles were shown to appear only under harsh, stressful conditions. Baxter validated a biophysical method (b) (4) which is now part of the release testing for rVWF Final Drug Product (FDP). (b) (4)
Additionally Baxter added the Mix2Vial (b) (4), which is included in the rVWF clinical kit. The family of Mix2Vial transfer devices are 510(k) cleared [510(k) # K031861] and CE marked. They are distributed by MEDIMOP Medical Products Ltd., a West Company. This (b) (4) will clear particles at point of care should they develop due to excessive shaking.

(b) (4)

(b) (4)

Reviewer's comments:

In other parts of the submission, numerous other lots were fully characterized and therefore, it is not clear which lots are designated as the conformance lots. Moreover, several changes were implemented in the manufacturing process, and therefore Baxter should clarify if the conformance lots are representative of the new process. Baxter should submit the analytical characterization of the lots individually tabulated. An IR was sent on 23 July, 2015.

IR #1:

You have described a total of (b) (4) rVWF conformance lots that were characterized using all the analytical tests. However, there is no comprehensive list of all the final drug product conformance lots that were manufactured using the current process. Please compile this list and include details about the origin of each of these lots and the physicochemical characterization and analytical test results, individually tabulated for each lot.

Baxter response to IR #1:

A comprehensive list of the (b) (4) final DP conformance lots that were manufactured using the current process and the origin of these lots, were provided in Table 1 and Table 2 of the amendment, copied here.

(b) (4)

Three DP conformance lots were subjected to physicochemical characterization; their test results are individually tabulated in Table 5 of the amendment. All other test results for the DP conformance lots appear in Section 3.2.P.5.4 *Batch Analyses*. (b) (4) conformance lots were subjected to physicochemical characterization. The results, individually tabulated, were provided in Tables 3 and 4.

Reviewer's comment

Baxter's response is complete.

(b) (4)

Impurities and clearance of process related impurities

Process-related impurities include materials introduced during either the cell culture or the purification processes. Baxter identified the following main process-related impurities including biological impurities, chemical impurities and other impurities:

- Host cell related impurities: CHO Host Cell Protein (tested by (b) (4) [redacted], and residual rFurin (b) (4) [redacted])
- Residual FVIII (tested by (b) (4) [redacted])
- Polysorbate-80

(b) (4)

Product-related impurities

The results of the following product related impurities (Table 13 section 3.2.S.3.2) are summarized and listed by a number of assays performed on different stages of the production.

(b) (4)

Reviewer's comment:

Product- and process-related impurities were assessed by a number of assays performed satisfactorily on different stages of the rVWF production.

Control of materials – biological origin

Compendial materials (non-biologic materials listed in pharmacopeias and non-biologic materials that are not listed in pharmacopeias) are tested in accordance to the specified pharmacopeia monographs either by the supplier, Baxter and/or qualified external laboratories. After a supplier has met the required qualifications, the raw material may be accepted based upon a review of the Certificate of Analysis (COA) and specified abbreviated confirmatory testing, e.g. identity.

The following two materials are used in production of rVWF and are of biological origin; (b) (4)

(b) (4)

Recombinant Furin (rFurin) (based on section 3.2.S.2.3), (b) (4)

(b) (4)

(b) (4)

Reviewer's comment:

The materials of biological origin that are used in the production of rVWF were well investigated and there is no further safety concerns regarding the use of these materials. (b) (4)

are reducing the safety concerns involved with using rFurin.

Control of Excipients

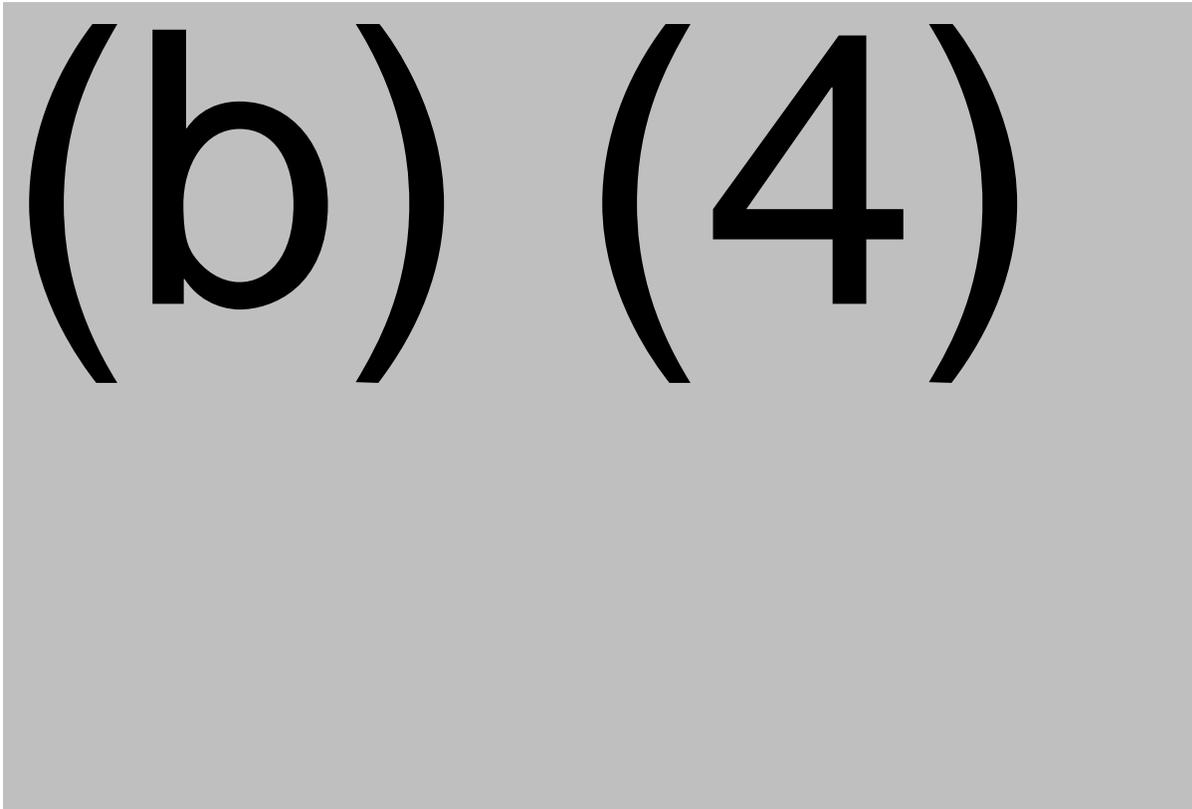
The excipients used in the pharmaceutical production of rVWF FDP are all compendial and listed in Table 1 of section 2.3.P.

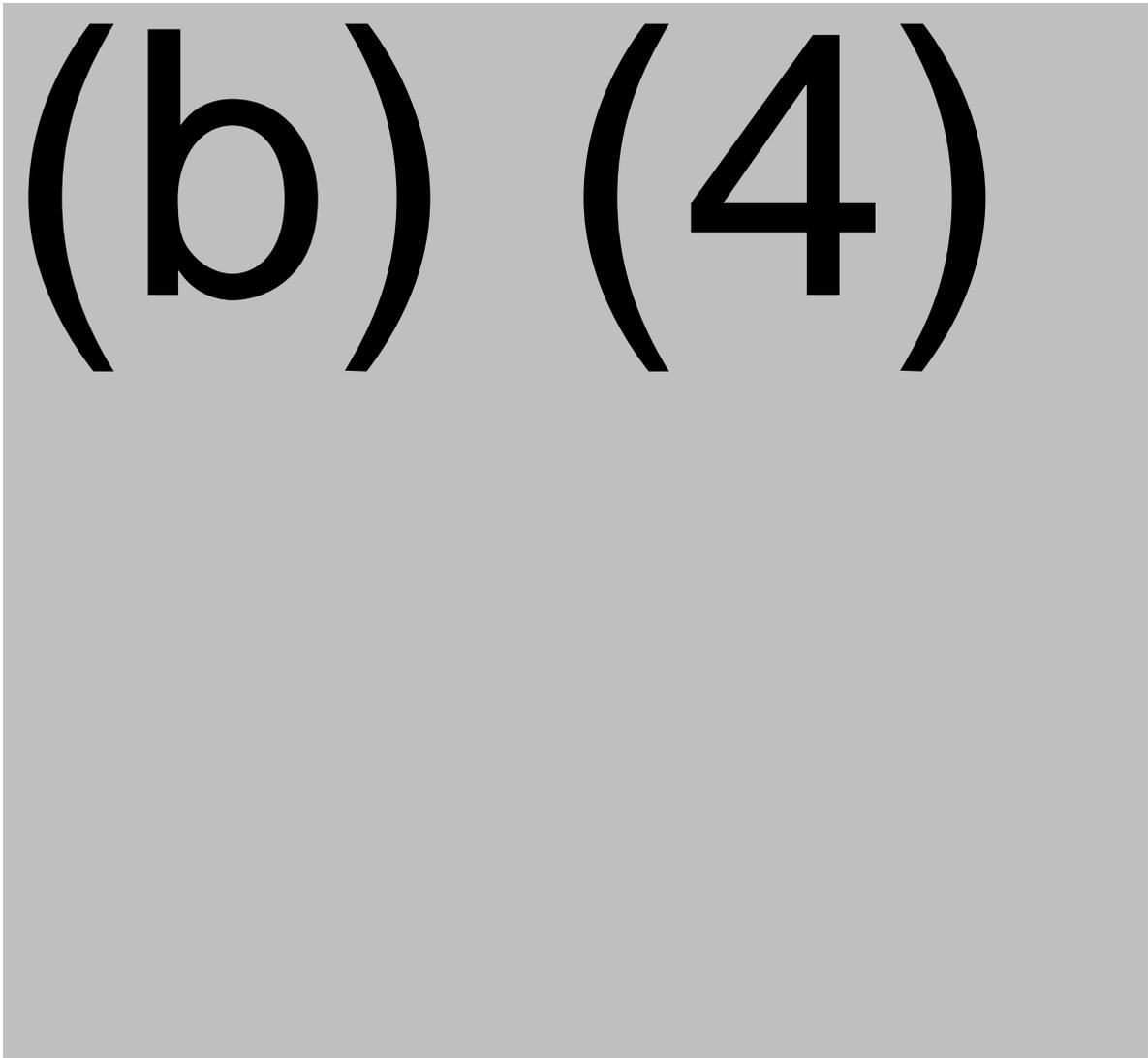
Table 1. Excipients

Excipient Description
Tri-sodium Citrate •2H ₂ O
Glycine
Mannitol
(b) (4) Polysorbate 80)
Trehalose •2H ₂ O
Water for Injections in Bulk

The excipients described in Pharmacopeias are tested to meet the requirements of (b) (4)
The Water for Injections in Bulk is manufactured to meet the requirements of (b) (4)

Analytical characterization of rVWF





The following parameters (and the acceptance criteria) are tested for the DP:

Parameter	Acceptance Criteria ^b
VWF:RCo Activity	(b) (4)
(b) (4)	(b) (4)
Sterility	Sterile
Endotoxin	(b) (4)
Appearance (lyophilized cake)	White to off-white friable powder

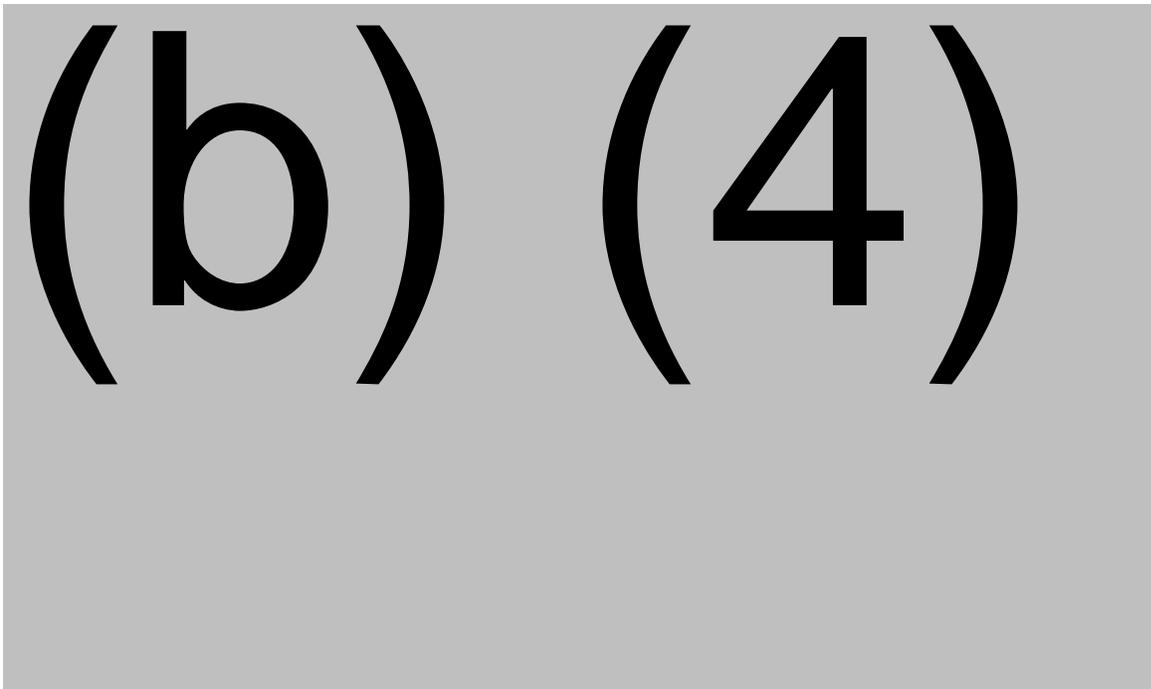
Appearance (reconstituted solution)	Clear, colorless solution, free from particles
Reconstitution Time	(b) (4)
(b) (4)	
Residual Moisture	
(b) (4)	
Particulate Matters ^g	
(b) (4)	
Citrate ^l	
Polysorbate-80 (b) (4)	
Glycine	
Sodium	
Mannitol	
Trehalose	

The results are detailed in section 3.2.S.3.1 and 3.2.P5.4.

Reviewer's comment:

The choice of assays and the results of the analytical characterization are satisfactory.

Drug substance and drug product specifications and justification



The proposed justifications for the DP testing are listed in Table 1 copied from section 3.2.P.5.6:

Table 1. rVWF FDP Final Drug Product

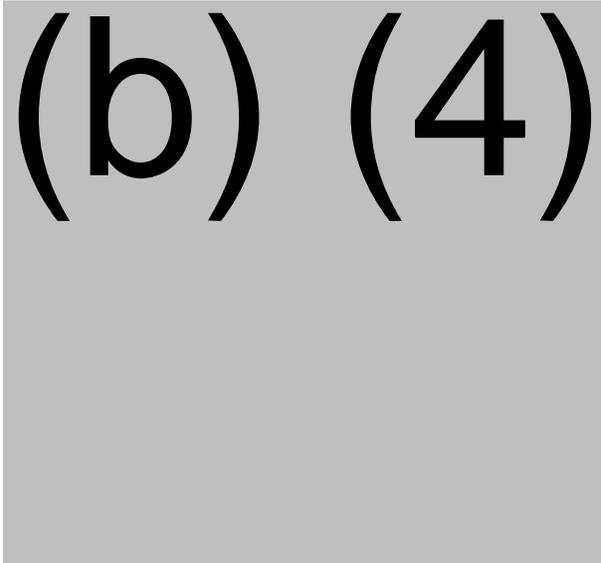
Test	Parameter Measured	Justification Summary	Section
VWF E.Co Activity	(b) (4)	(b) (4)	Section 3.2.P.5.6 Justification of Specification(s) [von Willebrand Factor Elongation Co-factor Activity (VWF E.Co)]
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) [VWF (b) (4)]
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) [Swirlity]
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) [Endotoxin]
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) [Appearance (Lyophilized Cake)]
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) [Appearance (Reconstituted Solution)]
Swirlity			Section 3.2.P.5.6 Justification of Specification(s) [Swirlity]
Endotoxin			Section 3.2.P.5.6 Justification of Specification(s) [Endotoxin]
Appearance (lyophilized cake)			Section 3.2.P.5.6 Justification of Specification(s) [Appearance (Lyophilized Cake)]
Appearance (reconstituted solution)			Section 3.2.P.5.6 Justification of Specification(s) [Appearance (Reconstituted Solution)]
Reconstitution Time			Section 3.2.P.5.6 Justification of Specification(s) [Reconstitution Time]
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
Residual Moisture			Section 3.2.P.5.6 Justification of Specification(s) [Residual Moisture]
(b) (4)			Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
Particulate Matter			Section 3.2.P.5.6 Justification of Specification(s) [Particulate Matter]

Test	Parameter Measured	Justification Summary	Section
(b) (4)	Identity	Clinical Experience and Process Capability	Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
(b) (4)	Purity	Process Capability, Clinical Experience	Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
(b) (4)	Safety	Process Capability, Clinical Experience	Section 3.2.P.5.6 Justification of Specification(s) (b) (4)
Citrate	General	Safety, Target Excipient Concentration	Section 3.2.P.5.6 Justification of Specification(s) [Citrate]
Glycine	General	Safety, Target Excipient Concentration	Section 3.2.P.5.6 Justification of Specification(s) [Glycine]
Mannitol	General	Safety, Target Excipient Concentration	Section 3.2.P.5.6 Justification of Specification(s) [Mannitol]
Polyorbate 80 (b) (4)	General	Safety, Target Excipient Concentration	Section 3.2.P.5.6 Justification of Specification(s) [Polyorbate 80 (b) (4)]
Trehalose	General	Safety, Target Excipient Concentration	Section 3.2.P.5.6 Justification of Specification(s) [Trehalose]
Sodium	General	Safety, Target Excipient Concentration	Section 3.2.P.5.6 Justification of Specification(s) [Sodium]

Statistical analysis was conducted for specification setting, when applicable. In the statistical analysis, process capability has been calculated using the K factor. To account for the small number of observations, K factor correction was used instead of 3 standard deviations (3σ) to expand the processing limits, according to the local procedure.

Reference Standards or Materials

A summary of external reference standards or materials that are commercially available for purchasing, testing and releasing rVWF DS and DP is provided in Table 1 of section 3.2.S.5.



Drug Product composition

Table 1. Drug Product Composition of the Von Willebrand Factor

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		
Manmitol	20g/L	20g/L		
Trehalose Dihydrate	10g/L	10g/L		
Glycine	15mM	15mM		
Polysorbate 80	0.1g/L	0.1g/L		

Drug Product - Container Closure

The rVWF DP is filled in a (b) (4) glass vial with a nominal capacity of 20 mL. The vial is closed with a (b) (4) rubber stopper (b) (4), and sealed with aluminum overseal and tamper proof snap off plastic cap. The vials conform to (b) (4) requirements for hydrolytic resistance. Sterile WFI manufactured at (b) (4) for the reconstitution of rVWF FDP is filled in a colorless (b) (4) glass vial and sealed with a (b) (4) rubber stopper (b) (4). Sterile WFI manufactured at Baxter (b) (4) for the reconstitution of rVWF FDP is filled in a colorless (b) (4) glass vial and sealed with a latex-free, (b) (4) rubber stopper. Container closure integrity, performed using an (b) (4) system, met acceptance criterion of no extraneous growth. Baxter qualified both container closure systems through small scale stability studies, extractables and leachables testing, container closure integrity and shipping studies.

Drug Product - product diluent

The rVWF FDP is reconstituted with a sWFI with a nominal volume of 10 mL and a minimum extractable volume of (b) (4). The sWFI is manufactured by (b) (4) or Baxter Healthcare Corporation (b) (4).

rVWF stability

(b) (4)

[Large redacted area covering the majority of the text in this section]

(b) (4)

rVWF DP stability studies

The testing parameters are listed in Table 1 of section *Drug Product Stability rVWF* (copied here). The results are summarized in section 3.2.P.8.1 of the application.

Table 1. Test Parameters for rVWF Forced Degradation Study

Attribute category	Analytical Method	Purpose
Potency	(b) (4)	Representative for routinely tested stability parameters
Identity/Purity	(b) (4)	
General Quality	(b) (4)	
	Visual Appearance	
	(b) (4)	
(b) (4)	(b) (4)	(b) (4)

Stability studies

The stability studies were carried out at the following conditions:

1. Routine storage temperature (5 °C ± 3 °C)
2. Room temperature (30 °C (b) (4) [redacted])
3. Accelerated conditions (b) (4) [redacted]
4. A temperature excursion study is being performed by simulating the excursion to 30 °C for up to (b) (4) [redacted] after storage at 5 °C for 18 months.

Table 9 of section 3.2.P.8.1 carries the details regarding (b) (4) lots that were put in the program. Table 11 describes the tested parameters. A summary of parameters is as follows:

- VWF:RCo activity
- (b) (4) [redacted]

(b) (4)

- Visual Appearance (lyophilized)
- Visual Appearance (reconstituted)
- Reconstitution Time

(b) (4)

- Particulate Matter
- Residual Moisture
- Sterility
- Endotoxins

The graphical and tabloid details are presented in subsection 3.6 of section 3.2.P.8.1.

Reviewer's comments

Three clinical Phase 3 rVWF FDP lots were tested for up to (b) (4) at 5 °C and 30 °C, as well as (b) (4) (b) (4) conformance rVWF FDP lots were tested for up to (b) (4) at 5 °C and 30 °C as well as (b) (4). All results were within the specifications with no noticeable trends. Baxter decided that from now on they will remove the (b) (4) test as part of the stability because it is not providing information that is relevant to the drug quality and other tests, such as the potency, (b) (4) cover better the quality of the protein. Baxter decision is acceptable.

Baxter pre-licensed inspection

The following CMC related 483s were issued to the (b) (4) facility:

1. The following standard operating procedures (SOP) for laboratory investigations are examples of deficient SOPs in which no limits are set as to the number of repeat that are allowed before a valid reportable result is reported or a Laboratory Investigation Report (LIR) is initiated:

SOP VN-20-03009, effective date 28.01.2015 entitled, (b) (4)

SOP VN-13-06113TB, effective date 06.08.2014 entitled, (b) (4)

SOP VN-13-06081TB, effective date 03.11.2014 entitled, (b) (4)

As a consequence, samples had been tested repeatedly until the results met the test validity criteria, without an investigation.

2. Deviation investigations are not well documented and poorly conducted, which led to ineffective corrective and preventive actions (CAPA). For example:

Recurring deviations were observed in the (b) (4). On November 2014 out of (b) (4) samples tested, 13 LIRs were initiated. However, in April 2015, out of (b) (4) samples tested, 39 resulted in LIRs (a 50% increase in the past six months) and a CAPA was initiated only on April 2015.

The following CMC related 483s were issued to the (b) (4) facility:

1. The following standard operating procedures (SOP) for laboratory investigations are examples of deficient SOPs in which no limits are set as to the number of repeat that are allowed before a valid reportable result is reported or a Laboratory Investigation Report (LIR) is initiated:
 - SOP OR-20-00088E, effective date 07.05.2014, describes the procedure for initiating and conducting an LIR,
 - SOP OR-13-00693, effective date 06.02.2014, describes the procedure for determination of purity and identity of rVWF using a (b) (4)

- SOP OR-14-00028E effective date 30.03.2015, describes the general procedure for appearance testing and SOP CE-13-00004 which describes the procedure for reconstituting for rVWF (which describes appearance testing).

As a consequence, samples had been tested repeatedly until the results met the test validity criteria, without an investigation. For example:

Control sample rVWF (b) (4)

[REDACTED]

2. Deviation investigations are not well documented and poorly conducted. For example (b) (4)

[REDACTED] VWF Final Drug Product lot (b) (4) . However, no investigation was performed merely because the risk was considered low.

On 1 June, 2015 Baxter's responded satisfactorily to the Agency's CMC observations listed on Form 483, which was issued at the conclusion of the pre-licensing inspection of Baxter's manufacturing facilities located in (b) (4) . Baxter will (b) (4)

[REDACTED]

The target date for completion of all actions described in the response is August 2015.