



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation Research
Office of Blood Research and Review

To: STN BL 125577/0 and Cherie Ward-Peralta
From: Zuben E. Sauna, CMC (Product) Reviewer
Applicant: Baxter
Product: Von Willebrand Factor (Recombinant)
Subject: Chemistry, Manufacturing and Controls Product Review
Through: Nancy, Kirschbaum, PhD, Acting Team Leader, OBRR/DHRR/LH
Tim Lee, PhD, Acting Chief, OBRR/DHRR/LH
CC: Chava Kimchi-Sarfaty, PhD, Chair of the review committee

Scope of review

The following topics pertaining to CMC (Product) have been reviewed by me:

- A. Drug Substance (DS)
 - Materials and reagents of non-animal/ non-human origin
 - Process development and validation
 - (b) (4) [REDACTED]
- B. Drug product (DP)
 - Description
 - Composition
 - Formulation development
 - Product attributes
 - Description of the manufacturing process and its control
 - Process development and validation

Introduction

Von Willebrand factor (VWF) is a large, multimeric glycoprotein. Deficiency in, or a non-functional VWF, results in Willebrand disease (VWD) which is the most common inherited human bleeding disorder. VWF is assembled from identical approximately 250 kDa subunits into disulfide-linked multimers that may be >20,000 kDa. The 250 kDa monomer is derived from the primary translation product of 2813 amino acids. This polypeptide includes: (i) a signal peptide of 22 residues, (ii) a large pro-peptide of 741 residues, and (iii) the mature subunit of 2050 residues.

Mutations in VWF can disrupt a complex biosynthetic process at several steps to impair the assembly, intracellular targeting, or secretion of VWF multimers. Other mutations impair the survival of VWF in plasma or the function of specific ligand binding sites. Thus, VWF mutations can result in several distinct VWD phenotypes. In addition, VWF is a carrier protein for blood coagulation factor VIII. When the VWF-factor VIII interaction is disrupted (or in the absence of VWF), factor VIII is rapidly removed from the circulation.

Thus, VWF performs two essential functions in hemostasis: it mediates the adhesion of platelets to subendothelial connective tissue, and it binds to blood coagulation factor VIII. Clinically, patients with severe VWD have undetectable levels of VWF and factor VIII levels that are <10% of normal. On the other hand, hemophilia A patients have low levels of factor VIII and normal levels of VWF. Currently marketed replacement therapies for patients with VWD include three available plasma-derived concentrates that contain the Factor VIII/vWF complex.

The applicant (Baxter Healthcare Corporation) has developed VONVENDI, a recombinant 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, (b) (4). Recombinant VWF is formulated as a lyophilized powder for intravenous administration after reconstitution with sterile water for injection. The proposed nominal dosage strengths are 650 and 1300 IU/vial. The proposed clinical use of VONVENDI is the prevention and treatment of bleeding episodes in adults (age 18 or older) diagnosed with VWD.

Drug substance

Support of the Manufacturing Process and Established Process Controls

Starting Materials

Materials of Animal or Human Origin

(See review by Chava Kimchi-Sarfaty)

Materials and Reagents of Non-animal/ Non-human Origin

Compendial (listed in Pharmacopeia) raw materials and reagents used during drug substance manufacture are listed in Table 1; these are provided in Module 3.2.S.2.3 of the submission.

Table 1: Raw Materials and Reagents (Compendial)

A] Materials/reagents used at the (b) (4)

(b) (4)

(b) (4)

Non-compendial (not listed in Pharmacopeia) raw materials and reagents used during drug substance manufacture are listed in Table 2 (below). These are provided in Module 3.2.S.2.3 of the submission.

Table 2: Raw Materials and Reagents (Non-compendial)

A] Materials/reagents used at the (b) (4)

(b) (4)

B] Materials/reagents used at the (b) (4)

(b) (4)

(b) (4)

Reviewer's comment: Baxter's procedures for vendor qualifications, agreements, audits, investigations and complaints and their resolution were evaluated during inspections of the facilities at (b) (4) and were deemed acceptable. In-house specifications for all non-compendial materials were submitted to the BLA.

Process Development and Validation

The manufacturing process development for rVWF Bulk Drug Substance (BDS) is described in Modules 3.2.S.2.6 and 3.2.S.2.4 of the BLA. The manufacturing process for rVWF was designed and developed through iterative risk assessment, quality characterization and process characterization cycles, with the objective of consistently producing a highly purified rVWF drug substance in a stable pre-formulated form that allows a robust final formulation and filling.

Manufacturing process (b) (4)

(b) (4)

(b) (4)

Risk assessment for process development

Baxter adopted a systematic approach to process development, identifying Critical Quality Attributes (CQA) and Critical Process Parameters (CPPs) based on the following criteria:

- Identifying the CQAs using a clinical hazard analysis based on “CQA Assessment” tool (RACT);
- Identifying the process steps, process parameters, and intermediate attributes of the manufacturing process and evaluating the criticality of the parameters;
- Identifying CPPs using a Process Failure Mode and Effects Analysis (PFMEA) based on “CPP Assessment” tool.

The following ranking was used to determine CPPs:

(b) (4)

Product and process impurities monitored during the development of the manufacturing process

During the development of the manufacturing process, the following product and process related

(b) (4)

Reviewer’s comment: Baxter has used standard procedures to identify potential impurities that present a potential clinical risk. The limits set for these impurities are reasonable based on clinical experience, reports in the literature and the sensitivity of currently available analytical methods to detect these impurities.

(b) (4)

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(b) (4)

Drug Product

Description

The recombinant von Willebrand Factor (rVWF) final drug product (FDP) consists of 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 product is supplied in single-dose vials with nominal dosage strengths of 650 or 1300 IU/vial. Sterile water for injection (WFI) for reconstitution and a Mix2Vial device are also provided. The container closure system consists of either a 10 mL (for the 650 IU/vial dose) or a 30 mL (for the 1300 IU/vial dose) (b) (4) glass vial with a (b) (4) rubber stopper (b) (4) , and sealed with an aluminum seal and tamper proof snap off plastic cap. The sterile WFI for the reconstitution of rVWF FDP is provided in a (b) (4) glass vial, and sealed with a (b) (4) rubber stopper (b) (4) . The Mix2Vial transfer device is provided for quick transfer of diluent into drug product vials and aspiration of reconstituted product into a syringe. The two vial adapters are provided pre-assembled and can be disassembled after diluent transfer and reconstitution. The product vial adapter stays on the product vial after disassembly and has a male luer, which can be connected to a luer lock syringe for easy transfer. The product side vial adapter (b) (4) of the product during aspiration. Baxter has conducted compatibility studies showing that the Mix2Vial device is compatible with the rVWF FDP and that no significant loss of

VWF:RCo activity occurs upon reconstitution (Module 3.2.P.2.6). The family of Mix2Vial devices are 510(k) cleared [510(k) # K031861].

Composition

The components present in the rVWF final drug product are listed below:

Component	Dosage strength		Function	Quality
	650 IU/vial	1300 IU/vial		
rVWF	130 IU/mL	130 IU/mL	(b)	(4)
Tri-Sodium Citrate Dihydrate	15mM	15mM		
Mannitol	20g/L	20g/L		
Trehalose Dihydrate	10g/L	10g/L		
Glycine	15mM	15mM		
Polysorbate 80	0.1g/L	0.1g/L		

Formulation Development

The initial FDP formulation development of rVWF is described in Section 3.2.P.2.2. Formulation of rVWF drug product was the same for all potencies and remained unchanged from Phase 1 to Phase 3 clinical investigations. The composition and function of the excipients is given above; listed below are product attributes considered during formulation development.

Selected CQA	Comment
Potency (RCo/mL)	(b) (4)
Appearance of reconstituted solution (color/turbidity/filaments)	
(b) (4)	
rVWF insoluble aggregates (subvisible particles)	
Yield	

Product Attributes

After defining the initial manufacturing process, assessments were performed on the process in order to identify key steps in the process for which specific experimental studies were performed for process characterization, optimization, and robustness. Critical quality attributes (CQA) and critical process parameters (CPPs) were identified and then used during clinical development to establish manufacturing controls and limits and to evaluate the impact of manufacturing process changes prior to implementation. The following critical quality attributes for each step of the rVWF Fill/Finish process were identified to be potentially impacted.

Process Step Name	Potentially impacted CQAs
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(b) (4)

Process Step Name	Potentially impacted CQAs
	<div>(b) (4)</div>
Sterile Filtration (SF)	
Aseptic Filling	
Lyophilization	
Capping	

Excipients and Their Control

The final drug product is formulated with tri-sodium citrate, glycine, mannitol, (b) (4) (Polysorbate 80), trehalose and water for injection. The table reproduced below summarizes control of excipients.

Compendial Excipient Description	Quality Standard
Tri-sodium Citrate •2H ₂ O	(b) (4)
Glycine	
Mannitol	
(b) (4) (Polysorbate 80)	
Trehalose •2H ₂ O	
Water for Injection	

Justification for the Proposed Release Specification

Justification for the subset of quality control tests chosen or not chosen for final release was provided in Module 3.2.P.5.6, Justification of Specifications. Specifications were defined in accordance with applicable pharmacopoeial requirements or the ICH Q6B guideline entitled, “*Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*.” Criteria used to establish acceptance ranges or limits are summarized below.

Test	Parameter	Justification Summary
VWF:RCo Activity	(b) (4)	(4)
(b) (4)		
Total Protein		
(b) (4)		
(b) (4)		
(b) (4)		
Sterility		
Endotoxin		
Appearance (lyophilized cake)		
Appearance (reconstituted solution)		
Reconstitution Time		
(b) (4)		
Residual Moisture		
(b) (4)		
Particulates		
(b) (4)		
(b) (4)		
Citrate		
Glycine		
Mannitol		
Polysorbate 80		
Trehalose		
Sodium		

All drug product lots used for the justification of specifications were manufactured according to the intended commercial manufacturing process at the Baxter facility located in Thousand Oaks, California, US. The full data set consists of (b) (4) lots (650 IU/vial and 1300 IU/vial) manufactured to support clinical investigation, (b) (4) of which resulted from the process qualification studies (conformance lots).

Release Specification

Baxter used characterization data and risk assessment to propose the final drug product release specification presented in module 3.2.P.5.1 and reproduced below:

Parameter	Test Method	Acceptance Criteria
VWF:RCo Activity	(b) (4)	(4)
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
Sterility	Visual	White to off-white friable powder
Endotoxin		
Appearance (lyophilized cake)	Visual	Clear, colorless solution, free from particles
Appearance (reconstituted solution)	Visual	
Reconstitution Time	(b) (4)	(4)
(b) (4)		
Residual Moisture		
(b) (4)		
Particulate Matters		
(b) (4)		
(b) (4)		
(b) (4)		
Citrate		
Polysorbate-80		
(b) (4)		
Glycine		
Sodium		
Mannitol		
Trehalose		

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Lyophilization

The lyophilization is performed according to the following a validated program outlined in Module 3.2.P.3.3 (Table 1).

Stoppering

(b) (4)

Unloading of Lyophilized Vials

(b) (4)

Capping and Laser Coding

(b) (4)

Storage of Lyophilized Product

The vials are transferred to a cold storage room (2°C to 8°C) after capping is complete.

(b) (4) Testing and Visual Inspection

(b) (4) testing is performed on the product using a (b) (4) inspection system, (b) (4) The system will detect the presence of (b) (4) in the vials and will automatically reject vials with (b) (4) levels that would indicate potential compromised container closure integrity. The vials are also 100% visually inspected for foreign material, glass, stopper, cap, and product cake defects. Upon completion of the (b) (4) testing and visual inspection, while awaiting labeling and packaging, the vials are stored in 2 to 8°C pending packaging into cardboard containers that prevent breakage of glass vials.

Vial and Unit Carton Labelers and Packaging Line Management System

The Vial Labeler, (b) (4), Unit Carton Labeler, (b) (4), Printer System, (b) (4), and Packaging Line Management System (PLMS), (b) (4), are installed on the Packaging Line. The Vial and Unit Carton Labelers and Printer System, along with the PLMS, are used for the placement and verification of labels on the product vial and unit carton.

Segregation and Label Control

Procedural segregation, through SOP TO-20-EN510, *Control of Multi-Product Manufacturing*, is used at the Thousand Oaks facility. Product segregation and cross-contamination between products/materials are controlled via line clearance, area approval, cleaning, and labeling requirements per facility SOPs.

Proposed commercial batch sizes

The process qualification established acceptable manufacturing batch sizes of (b) (4) 650 IU/vial (b) (4) 1300 IU/vial).

Batch formula

The final drug product is available in two nominal dosage strengths, 650 IU or 1300 IU per vial, filled from a single batch formula whose composition is given below.

Component and Quality Standard	Target Concentration
von Willebrand Factor	130 IU/mL
Na ₃ Citrate•2H ₂ O (USP, EP, JP)	15mM
Mannitol (USP, EP, JP)	20 g/L
Trehalose •2H ₂ O 2 (USP, EP, JP)	10 g/L
Glycine (USP, EP, JP)	15mM
Polysorbate 80 (USP, EP, JP)	0.1 g/L
Total	n/a

(b) (4)

FDP Lots Produced During Phase 1 and Phase 3 Clinical Trials

An overview of all FDP lots produced during Phase 1 and Phase 3 clinical trials with their potencies, batch sizes, and use are summarized below.

Lot No.	Nominal Potency [IU/vial]	Used for
VNH1G001	(b) (4)	Phase 1
VNH1G002	(b) (4)	Phase 1
VNH1H001	(b) (4)	Phase 1
VNH1H002	(b) (4)	Phase 1
(b) (4)	(b) (4)	(b) (4)
(b) (4)	650	(b) (4)
(b) (4)	650	Phase 3 Intended
TVA11002A	650	Phase 3
TVA11003A	650	Phase 3
TVA12001A	650	Phase 3
TVA12002A	650	Phase 3

(b) (4)

Lot No.	Nominal Potency [IU/vial]	Used for
TVA12003A	1300	Phase 3
TVA12004A	1300	Phase 3
TVA12005A	1300	Phase 3
TVA13001A	650	Phase 3

(b) (4)

Conclusion

All CMC (product) issues related to the scope of this review (outlined at the onset) of BL STN 125577/0 have been resolved. Pending resolution of review issues from other disciplines and other CMC reviewers, the application may be approved.