



MEMORANDUM

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

Date: May 11, 2007

To: File

From: Nancy Kirschbaum

Subject: Mid-cycle review memo: Original BLA, STN 125251.0 Octapharma Pharmazeutika Produktions GmbH, for von Willebrand Factor Concentrate (Human)

CC: Tim Lee
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Applicant: Octapharma Pharmazeutika Produktions GmbH, 235 Oberlaaer Strasse, A-1100 Vienna, Austria. Contact: Dr. Barbara Rangetiner, 011-431-61032-266

Indication for Use: "WILATE is indicated in adult and pediatric patients for the treatment -(b)(4)-
----- of spontaneous and trauma-induced bleeding episodes in severe von Willebrand
disease (vWD) and in mild and moderate vWD where use of DDAVP (1-deamino-8-D-arginine
vasopressin/desmopressin) treatment is ineffective or contraindicated. ----- (b)(4)-----
-----"

3.2.S Drug Substance

3.2.S.1: Description: Human plasma-derived concentrate of von Willebrand Factor/Factor VIII (vWF/FVIII), double virus inactivated and freeze-dried. Final product is offered in two nominal dosages: -(b)(4)- IU or -(b)(4)- IU vWF ristocetin cofactor activity (vWF:RCO; hereafter, referred to as vWF potency) per vial. The -(b)(4)- IU vWF potency vial will also contain nominal 450 IU FVIII activity (determined by chromogenic assay). The -(b)(4)- vWF potency vial will also contain nominal 900 IU FVIII activity. Final product is reconstituted in WFI containing 0.1% polysorbate 80 to final vWF target potency, -(b)(4)-.

3.2.S.2: Drug Substance Manufacture: Octapharma defined drug substance as that which is synthesized and/or added during drug product manufacture. As such, details of drug substance manufacture and control were documented under sections designated in the CTD for drug product. This review memo will document as closely as possible review of drug substance manufacture and control within the original framework of the CTD.

One (1) page determined to be non-releasable: (b)(4)3.2.S.2.2 Manufacturing Summary (see

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

3.2.S.2.3 Control of Raw Materials and Reagents:

Plasma: U.S. based plasmapheresis centers and community blood banks in compliance with 21 CFR 640.30 (single donor/recovered plasma) or 21 CFR 640.60 (Source Plasma, Human). "Plasma" under 21 CFR 640.30 is intended for transfusion not for further manufacture in the absence of a short supply agreement under 21 CFR 601.22. Furthermore, 21 CFR 640.30 describes a number of plasma products collected and stored under different conditions. Finally, the following publication from Octapharma AG: Josic D, Buchacher A, Kannicht C, Lim Y-P, Loester K, Pock K, Robinson S, Schwinn H, Stadler M. Degradation products of FVIII which can lead to increased immunogenicity. Vox Sang. (1999)77 suppl. 1: 90-99, reported the observance of a 40 kDa degradation product in FVIII batches manufactured with recovered plasma that was correlated with occurrence of FVIII inhibitors in previously treated patients. Information about blood collection centers, short supply agreement for recovered plasma source material, and comparability between product manufactured with Source or recovered plasma was requested during 15 March 2007 teleconference. Octapharma internal quality control procedure for Cryoprecipitate (section 3.2.P.4) -----(b)(4)-----

Amendment 0.4 responses to information about plasma source material requested during 15 March 2007 teleconference:

1. None of the conformance lots was produced from recovered plasma.
2. None of the non-clinical lots was produced from recovered plasma
3. Lot 436 006 181, used in clinical study, TMAE 104, was produced from recovered plasma.
4. A list of blood collection centers was provided.
 - a. Umbrella organizations for recovered plasma: -----(b)(4)-----
 - b. Umbrella organization for Source plasma: -----(b)(4)-----
5. A list of virus screening test kits used and laboratories performing testing was provided.
6. Short supply agreement template between Octapharma AG and -----(b)(4)-----
----- Section 2. Quantity Provided, lists options for plasma types based on time to freezing: (1) -(b)(4)- (2) -(b)(4)- (3) -(b)(4)- (4) -(b)(4)-
7. Master Contract Attachment 3: QA Agreement and Plasma Specifications (amendment to Short supply agreement)- Section 8 describes collection and storage (freezing) requirements for different options specified in Section 2, Short supply agreement. Freezing method is specified: -----(b)(4)-----; freezing procedure must be standardized and validated. -----(b)(4)-----
----- The collection/freezing option for recovered plasma intended for manufacture into vWF concentrate was not specified.
8. Final release testing results for lots -----(b)(4)----- manufactured from European recovered plasma for distribution in Europe were provided. Analytical comparability between Source Plasma and Recovered Plasma derived lots through extensive biochemical characterization was not investigated.

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

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

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3.2.S.2.5 Process Evaluation/Validation- see 3.2.P.5

3.2.S.2.5.6 Hold Times (see 3.2.P.3.4.1)

Manufacturing Step	Hold Times/Temperatures	Supportive Investigations
Cryoprecipitate	----- (b)(4) ----- -----	Report OC06-0028† Protocol FFH0604

†see 3.2.P.3.4, Performed at Octapharma ----- (b)(4) -----

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--(b)(4)--
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3.2.S.3 *Characterization*: The following published report was submitted to the BLA: Stadler M., Gruber G, Kannicht C, Biesert L, Radomski KU, Suhartono H, Pock K, Neisser-Svae A, Weinberger J, Roemisch J, Svae T-E. Characterisation of a novel high-purity, double virus inactivated von Willebrand Factor and Factor VIII concentrate (Wilate). Biologicals (2006) 34: 281-288.

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vWF Parameters I (3.2.P.5.5)

Lot/Potency	FVIII	vWF:RCo	vWF:RCo/FVIII
	CS	Agglut.	Calculated
	IU/ml	IU/ml	IU/IU
----(b)(4)----	77	90	1.17
----(b)(4)----	90	90	1.00
----(b)(4)----	94	90	0.96
----(b)(4)----	79	94	1.19
----(b)(4)----	79	84	1.06
----(b)(4)----	83	84	1.01
Mean Value	83.7	88.7	1.06

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--(b)(4)--
]

Process related impurities (3.2.P.5.5)

Impurity	Level
TnBP	---(b)(4)--
Octoxynol-9	---(b)(4)----
Inorganic ions (e.g. aluminum)	---(b)(4)-----
Leachables from chromatographic resins	---(b)(4)-----

3.2.S.4 Control of Drug Substance:

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

One (1) page determined to be non-releasable: (b)(4)

(b)(4)

3.2.P.1 Description:

Component	Quantity/vial		Function
vWF	-(b)(4)-	-(b)(4)-	Active ingredient
FVIII	450 IU	900 IU	Active ingredient
Protein	≤7.5 mg	≤15.0 mg	----
Glycine	50 mg	100 mg	----- (b)(4) -----
Sucrose	50 mg	100 mg	---- (b)(4) ----
NaCl	117 mg	234 mg	-(b)(4)-
Na-citrate 2H ₂ O	14.7 mg	29.4 mg	-(b)(4)-
CaCl ₂ 2H ₂ O	0.8 mg	1.5 mg	-(b)(4)-

3.2.P.2.1 Drug Substance	See Report under 3.2.P.7
3.2.P.2.2 Drug Product	
3.2.P.2.3 Manufacturing Process Development	
3.2.P.2.4 Container/Closure System	
3.2.P.2.5 Microbiological Attributes	

Report 6MS1030: Compatibility of the --(b)(4)-- set with Wilate (November 2006)- --(b)(4)--
infusion set is manufactured by -----(b)(4)-----

Test articles: Final container, 450 IU FVIII; Batch -----(b)(4)----- that had a high vWF. Sample potencies, FVIII by SOP263 (chromogenic assay) and vWF by SOP056 (platelet agglutination), were measured -----(b)(4)-----

Results presented indicated no decrease of vWF or FVIII potency with manipulation. The time period for experimental manipulations and drawing of samples was not provided. It did not appear that a long term incubation of reconstituted vWF concentrate in the infusion set components was evaluated. The presence of potentially leaching substances was not assessed.

Report 6MS1031: Compatibility of the Mix2Vial transfer set with Wilate (November 2006)- Mix2Vial transfer set is manufactured by Medimop Medical Projects, Ltd. Raanana, Israel. A similar experiment to that described (above) for the --(b)(4)-- set was performed with similar results.

3.2.P.2.7 Pharmaceutical Development Report (September 2006)- Octapharma has been developing FVIII/vWF concentrates for two decades with developmental goals: virus safety, product purity, and vWF stability. According to the report, Wilate is the sixth generation product with two virus inactivation steps and a novel anion exchange chromatography purification step. The second virus inactivation step, dry heat treatment replaced the -----(b)(4)----- step used in the fourth generation product, Octavi SDP, after reports of FVIII inhibitor outbreaks following treatment with Octavi SDP in Germany and Belgium in the early 1990's. A manufacturing flow chart and narrative were provided. The most recent process development was performed with reference to the 5th generation, Octanate, procedure.

- [illegible]

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

3.2.P.3 Manufacture:

3.2.P.3.1: Manufacturing sites

Name and Address	Responsibility	FDA Establishment Number
Octapharma Pharmazeutika Produktions GmbH A-1100 Vienna, Austria	Drug substance and product manufacture	3002809097
----- (b)(4) ----- ----- ----- -----	----- (b)(4) -----	
----- (b)(4) ----- ----- -----	----- (b)(4) -----	

3.2.P.3.2: Batch Formula-

Batch size- -----(b)(4)----- plasma per batch cryoprecipitate; -(b)(4)- cryoprecipitate per batch vWF concentrate

Four (4) pages determined to be non-releasable: (b)(4)

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

Final Container Quality Control (see also 3.2.P.5.4 Batch Analyses)

Specification		Conformance Lot			
Parameter	Limit	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
-(b)(4)-----	Conforms	Yes	Yes	Yes	Yes
-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
-(b)(4)---	------(b)(4)-----	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
-(b)(4)-----	------(b)(4)-----	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
Protein	-----(b)(4)---	0.9	0.9	0.8	0.9
-(b)(4)-----	-----(b)(4)---	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
	-----	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile
Moisture	-(b)(4)-	1.1	0.9	1.2	1.0
FVIII	-----(b)(4)---	89	82	79	83
-(b)(4)-----	--(b)(4)--	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
vWF:RCo	-----(b)(4)---	90	94	84	84
Glycine	------(b)(4)-----	9.8	10.5	10.1	10.0
Sucrose	------(b)(4)-----	9.1	10.0	10.0	10.1
Chloride	------(b)(4)-----	397	429	399	410
Sodium	------(b)(4)-----	411	423	405	417
Calcium	------(b)(4)-----	1.6	1.2	1.0	1.0
Citrate	------(b)(4)-----	11	11	10	11
TnBP	-(b)(4)-	<1	<1	<1	<1
Octoxynol	--(b)(4)--	<5.0	<5.0	<5.0	<5.0
General Safety	Pass	Pass	Pass	Pass	Pass
Endotoxin	---(b)(4)---	<0.15	<0.15	<0.15	<0.15
-(b)(4)-----	---(b)(4)---	-(b)(4)-	-(b)(4)-	-(b)(4)-	

3.2.P.4 Control of Excipients:

Compendial excipients: CaCl₂·2H₂O, Glycine, Sucrose, NaCl, Na₃citrate·2H₂O

3.2.P.5 Control of Drug Product:

Lot Numbering System

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

3.2.P.5.1 Specification 013FPS181/00/US (after reconstitution with 0.1% polysorbate 80 diluent according to PI)

Parameter	Limit	Method
-(b)(4)-----	White, pale yellow powder	-(b)(4)-
-(b)(4)-	-(b)(4)-	-(b)(4)-
-(b)(4)---	------(b)(4)-----	-(b)(4)-
-(b)(4)-----	------(b)(4)-----	-(b)(4)-
Protein	-----(b)(4)----	--(b)(4)--
-(b)(4)-----	-----(b)(4)----	-(b)(4)-
Moisture	-(b)(4)-	------(b)(4)----
FVIII activity	-----(b)(4)----	Ph. Eur. (CS)
-(b)(4)-----	-----	
vWF R:CoF	-----(b)(4)----	Ph. Eur. (R:Co)
Glycine	------(b)(4)-----	-(b)(4)-
Sucrose	------(b)(4)-----	-(b)(4)-
Sodium	------(b)(4)-----	------(b)(4)-----
Calcium	------(b)(4)-----	------(b)(4)-----
Citrate	-----(b)(4)----	-(b)(4)-
Chloride	------(b)(4)-----	------(b)(4)-----
TnBP	---(b)(4)--	-(b)(4)-
Octoxynol	-----(b)(4)--	-(b)(4)-
Endotoxin	-----(b)(4)----	---(b)(4)---
Sterility	sterile	21 CFR 610.12
General Safety	Pass	21 CFR 610.11

3.2.P.5.3 Validation of Analytical Procedures

Method	SOP	Validation Adequate
Visual Inspection	130SOP006	N/A
-(b)(4)-	130SOP028	√
-(b)(4)---	130SOP006	√
-(b)(4)-----	130SOP008	√
-(b)(4)---- Protein	130SOP059	√
-(b)(4)-----	130SOP132	√
Moisture	130SOP130	√
Sterility	130SOP120	√
FVIII CS	130SOP263	√
vWF R:Co	130SOP056	√
General Safety	137SOP028	√
Glycine	130SOP161	√
Sucrose	130SOP168	√
Sodium	130SOP029	√
Calcium	130SOP029	√
Citrate	130SOP032	√
Chloride	130SOP131	√
TnBP	130SOP153	√
Octoxynol	130SOP090	√
-(b)(4)-	130SOP062	√

3.2.P.6 Reference Standards or Materials: vWF potency reference standard used in the vWF:RCo activity assay is an in-house standard calibrated against the WHO 1st IS for vWF concentrates (00/514). Procedures for establishment and maintenance of in-house vWF reference standards were not provided.

3.2.P.7 Container Closure System:

	Vial	Stopper	Crimp Cap (Flip-Off)
Supplier	----- (b)(4) ----- -----	----- (b)(4) ----- -----	----- (b)(4) ----- -----
Material	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
Dimensions	-(b)(4)-	-(b)(4)-	-(b)(4)-

References for relevant Drug Master Files:

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

- -----

- -----

Report 03P007: Container/Closure integrity was validated by performing bacterial ingress studies on vials from three final product lots after storage for ----- (b)(4) ----- . All vials tested remained sterile.

3.2.P.8 Stability: Claimed shelf life- 24 months, 2-(b)(4)-°C within which time product may be stored for six months at room temperature (up to 25°C).

Stability upon reconstitution from Pharmaceutical Development Report (see 3.2.P.7)- Development studies investigated quality attributes and dissolution properties upon reconstitution with WFI or WFI with varying concentrations of polysorbate 80. Quality attributes were monitored by ----- (b)(4) ----- . According to Merck, the LD₅₀ for polysorbate 80 is 25,000mg/kg. Product development studies indicated >80% remaining FVIII activity -(b)(4)- after reconstitution in 0.1% polysorbate 80.

Reconstitution Devices (3.2.P.7.2)

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

[
--(b)(4)--
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Mix2Vial- [K031861; cleared 29 July 2003; 21 CFR 880.5440]:

Description: 20 mm vial adapter with filter at the drug-vial end and a 20 mm blue vial adapter at the diluent-vial end.

Materials:

Vial adapter body 20 mm Male connector blue	----- (b)(4) ----- -----
Vial adapter body 20 mm	----- (b)(4) ----- -----
15 µm filter	----- (b)(4) -----
Filter Material	-(b)(4)-
Sterilization	----- (b)(4) -----
Compatibility	----- (b)(4) ----- -----

Validation data were not submitted

Labeling

- Prescribing Information: separate document with track changes
- Vial labels state shelf life, 24 months, 2-8°C and 6 months at room temperature whereas carton labels properly state the provision for 6 months at room temperature within the 24 month shelf life.
- Vial and carton labels inappropriately indicate FVIII potency (determined by chromogenic assay) in addition to vWF potency.
- Carton labels indicate a U.S. License number (i.e. K031861) for the MIX2VIAL transfer device. The number is a 510(k) application number that should not appear on product labels.

Product Diluent- 0.1% Polysorbate 80 in WFI

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

3.2.P.1 Description:

Composition

	5 ml vial	10 ml vial	Function
WFI	5,000 mg	10,000 mg	Solvent
Polysorbate 80	5 mg	10 mg	Solubilizer

3.2.P.3 Manufacture:

Batch Formula- For ----- (b)(4) -----

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

3.2.P.3.5 Process Validation

Conformance Lots:

Batch No.	DOM; fill size	Bulk Batch No.; Weight
---(b)(4)---	August 2006; 5 ml	----- (b)(4) -----
---(b)(4)---	August 2006; 10 ml	----- (b)(4) -----
---(b)(4)---	August 2006; 10 ml	----- (b)(4) -----
---(b)(4)---	August 2006; 5 ml	----- (b)(4) -----
---(b)(4)---	August 2006; 10 ml	----- (b)(4) -----
---(b)(4)---	August 2006; 5 ml	----- (b)(4) -----

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

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

[
 --(b)(4)--
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3.2.P.5 Control of Drug Product:

Lot Numbering System

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

Source of Component

Component	Supplier	QA/QC
WFI	----- (b)(4) -----	QA Agreement/ Octapharma release
Polysorbate 80	----- (b)(4) -----	Supplier CofA; Octapharma receipt inspection/identity test

Octapharma AB stated compliance with TSE guideline, EMEA 410/01 in that no materials of bovine origin are used for manufacture of solvent (see 3.2.P.4.5)

3.2.P.5.1 (Final Container Release) Specification

Parameter	Limit	Method
Polysorbate 80 content	----- (b)(4) -----	----- (b)(4) -----
-(b)(4)-	-(b)(4)-	----- (b)(4) -----
-(b)(4)-----	---- (b)(4) ---	----- (b)(4) -----
-(b)(4)-----	----- (b)(4) -----	----- (b)(4) -----
-(b)(4)----	---- (b)(4) --	----- (b)(4) -----
Endotoxin	----- (b)(4) -----	----- (b)(4) -----
Sterility	Sterile	----- (b)(4) -----
-(b)(4)-----	----- (b)(4) -----	--- (b)(4) --

3.2.P.5.2 Analytical Procedures

Method	SOP	Validation
TVC- Microbiological Examination of non-sterile products by ----- (b)(4) -----	131SOP008	√
Visual inspection of liquids and freeze-dried products...	130SOP006	
Determination of Polysorbate 80 by --- (b)(4) ---	130SOP049	M3068800.BE R
----- (b)(4) -----	130SOP028	00VAL028
----- (b)(4) -----	130SOP016	00VAL016
----- (b)(4) -----	130SOP039	00VAL039
Limit test for -(b)(4)- acc. -(b)(4)-	130SOP095	00VAL095
----- (b)(4) -----	130SOP062	00VAL062
Test for Sterility by ----- (b)(4) ---	131SOP120	00VAL106
----- (b)(4) -----	130SOP089	

3.2.P.6 Reference Standards or Materials: Polysorbate 80 -(b)(4)-

3.2.P.7 Container Closure System:

	Vial	Stopper	Crimp Cap
Supplier	---- (b)(4) ----	----- (b)(4) -----	----- (b)(4) -----
Material	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----

Dimensions	-(b)(4)-	-(b)(4)-	-(b)(4)-

3.2.P.8 Stability:

Stability claim-

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

Stability data- **No stability data were submitted.** Octapharma submitted a long term stability protocol and stated a commitment to provide stability data on an on-going basis. A stability study was initiated in September 2006.

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

[
--(b)(4)--
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3.2.P.3 Manufacture:

3.2.P.3.1 Finished product testing for endotoxin and sterility is performed by -----(b)(4)---

Batch Formula- (1) -----(b)(4)-----

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

3.2.P.3.5 Process Validation

Conformance Lots:

Batch No.	DOM; fill size
-(b)(4)-	05 May 2000, 5 ml
-(b)(4)-	05 May 2000, 5 ml
-(b)(4)-	05 May 2000, 5 ml

-(b)(4)-	05 May 2000, 10 ml
-(b)(4)-	05 May 2000, 10 ml
-(b)(4)-	05 May 2000, 10 ml

Two (2) pages determined to be non-releasable: (b)(4)

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

3.2.P.5 Control of Drug Product:

Lot Numbering System

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

Source of Component

Component	Supplier	QA/QC
WFI	-(b)(4)-	Internal
Polysorbate 80	suppliers not provided	-(b)(4)- receipt inspection

-(b)(4)- stated compliance with TSE guideline, EMEA 410/01 in that no materials of bovine origin are used for manufacture of solvent (see 3.2.P.4.5)

3.2.P.5.1 (Final Container Release) Specification

Parameter	Limit	Method
Polysorbate 80 content	----- (b)(4) -----	----- (b)(4) -----
-(b)(4)-	-(b)(4)-	----- (b)(4) -----
-(b)(4)-----	---- (b)(4) --	----- (b)(4) -----
-(b)(4)-----	----- (b)(4) -----	----- (b)(4) -----
-(b)(4)-----	----- (b)(4) -----	----- (b)(4) -----
-(b)(4)-----	---- (b)(4) --	----- (b)(4) -----
Endotoxin	----- (b)(4) -----	----- (b)(4) -----
Sterility	Sterile	----- (b)(4) -----
-(b)(4)-----	----- (b)(4) -----	-- (b)(4) --

3.2.P.5.2 Analytical Procedures

Method	SOP	Validation
TVC- Microbiological Examination of non-sterile products by plate count method according to ---- (b)(4) ---	131SOP008	√
Visual inspection of liquids and freeze-dried products...	130SOP006	
Determination of Polysorbate 80 by --- (b)(4) ---	130SOP049	M3068800.BE R
----- (b)(4) -----	130SOP028	00VAL028
----- (b)(4) -----	130SOP016	00VAL016
----- (b)(4) -----	130SOP039	00VAL039
----- (b)(4) -----	130SOP095	00VAL095
----- (b)(4) -----	130SOP108	00VAL108
-----	130SOP062	00VAL062
Test for Sterility ----- (b)(4) ---	131SOP120	00VAL106

------(b)(4)-----	130SOP089	
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3.2.P.6 Reference Standards or Materials: In-house batch ----(b)(4)----

3.2.P.7 Container Closure System:

	Vial	Stopper	Crimp Cap
Supplier	------(b)(4)-----	-----(b)(4)----	------(b)(4)-----
Material	------(b)(4)-----	------(b)(4)-----	------(b)(4)-----
Dimensions	-(b)(4)-	-(b)(4)-	-(b)(4)-

3.2.P.8 Stability:

Stability claim-

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

Stability data- Studies performed on conformance lots (plus others)

Stability conditions studied:

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

Predicted stability consequences:

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

Analysis

Test	Limit	Schedule
-(b)(4)-----	Clear, colorless, odorless, no particulates	All time points
Polysorbate 80	-----(b)(4)----	All time points
-(b)(4)-	-(b)(4)-	All time points
-(b)(4)-----	-----(b)(4)----	All time points
Endotoxin	-----(b)(4)----	Selected time points
Sterility	Sterile	Selected time points
Volume	Nominal	Selected time points
Pyrogens	Pyrogen free	Selected time points

Results

All data were graphed and trended. The stability claim: (1) ------(b)(4)-----

----- was supported by measured values of stability indicating parameters. Out-of-specification results for ------(b)(4)----- were observed beyond the stated stability claim. Although, measured values for polysorbate 80 were within specification after ------(b)(4)-----, lower confidence limits often exceeded specification. **It may be recommended that the storage claim at 2-8°C be shortened to ---(b)(4)---**

Comments for Mid-cycle Information Request

1. Regarding your manufacturing procedure:
 - a. -----(b)(4)-----

2. Your Short Supply Agreement for procurement of recovered plasma listed options for plasma types based on time to freezing: (1) -(b)(4)- (2) -(b)(4)-., (3) -(b)(4)-. or (4) -(b)(4)-; however, it did not stipulate the plasma type required for manufacture of vWF concentrate. Please amend the Short Supply Agreement to define the freezing time requirement for recovered plasma for further manufacturing use into vWF concentrate.
3. Regarding your product labeling:
 - a. Please change the established name of your product from Factor VIII/von Willebrand Factor complex to von Willebrand Factor concentrate (Human).
 - b. Please amend the Dosage and Administration section of the Full Prescribing Information (FPI) to provide recommendations for treating von Willebrand Disease based on vWF potencies.
 - c. Please eliminate references to Factor VIII (FVIII) as an active ingredient and references to FVIII potency values; you may include in the product description section of the FPI your experimentally determined ratio of FVIII to vWF potency.
 - d. Please remove the reference 510(k) number, K031861, for MIX2VIAL reconstitution device from the carton label. It is not a U.S. license number.
4. Please provide the date of manufacture for each conformance lot.
5. Please provide your procedures for establishment and maintenance of in-house von Willebrand Factor potency reference standards.
6. Please provide validation data for the performance of ---(b)(4)-- and Mix2Vial reconstitution devices.
7. Please provide suppliers of polysorbate 80 used in the reconstitution solvent.
8. Please provide time and temperature limits used during each step of 0.1% polysorbate 80 solvent manufacture.
9. The stability data submitted for -(b)(4)- 0.1% polysorbate 80 solvent indicated that lower confidence limits for polysorbate 80 content exceeded specification between --- (b)(4)--- storage. Please consider labeling the solvent with a ----(b)(4)--- dating period.
10. Please submit protocol template for FDA/CBER lot release.
11. Please submit a formal application for review of your proprietary name to FDA/CBER/OCBQ/DCM/APLB.
12. Please submit 20 vials of each conformance lot accompanied by completed lot release protocols to:

Please include a reference to STN 125251.0 when submitting sample vials and protocol.