



MEMORANDUM

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

To: File of STN 125251/0 & Pauline Cottrell

From: Nancy Kirschbaum & Tim Lee

Through: Basil Golding, M.D.
Director, Division of Hematology

Subject: Final Review of CMC information in the original BLA from Octapharma Pharmazeutika Produktions GmbH, for von Willebrand Factor/Coagulation Factor VIII Complex (Human) [Wilate]

This memorandum summarizes the review of the Chemistry, Manufacturing and Controls (CMC) information in Octapharma's biologics license application (BLA) for their von Willebrand Factor/Coagulation Factor VIII Complex (Human) under the proprietary name of Wilate. Dr. Nancy Kirschbaum was the original chairperson of the review committee. Upon her departure in September 2007, the file was transferred to me. At Mid-cycle, an Information Request was communicated to Octapharma on 15 May 2007. Octapharma responded in Amendment # 8 dated 4 June 2007. Since then, there were several teleconferences with Octapharma to request additional information and clarification. Reviews of which are summarized in the relevant sections below.

The major CMC issue in this review is the discrepancies in the VWF:RCo potency values derived from the manual and automated methods. This could be attributed to the nature of the VWF molecule in this product. Similarly, the VWF:RCo values in patient plasma in the Pharmacokinetics (PK) studies were deemed not interpretable. Together with other unresolved issues related to the clinical studies, the review committee recommends that a complete response (CR) letter be issued to Octapharma describing the deficiencies. A CR letter was thus issued on 8 January 2008.

Octapharma responded to the CR letter in an amendment dated 3 June 2009, and together with information submitted in subsequent amendments satisfactorily addressed all the CMC issues in the letter. Therefore, this BLA can be approved from a CMC perspective.

SUMMARY OF REVIEW

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

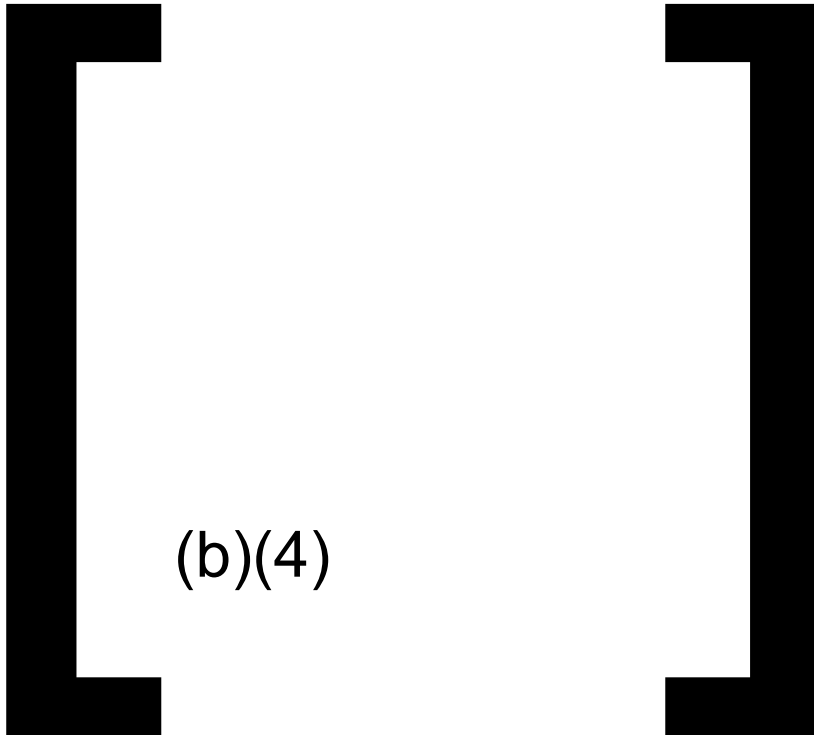
Indication for Use: “WILATE is indicated in adult and pediatric patients for the treatment ----(b)(4)---- of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease (VWD) and in mild and moderate VWD where use of DDAVP (1-deamino-8-D-arginine vasopressin/desmopressin) treatment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

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: 450 IU or 900 IU VWF ristocetin cofactor activity (VWF:RC₀; hereafter, referred to as VWF potency) per vial. The 450 IU VWF potency vial will also contain nominal 450 IU FVIII activity (determined by chromogenic assay). The 900 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.

[(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)-----

-----.
- 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.

Comments: Since Octapharma indicated that they currently uses recovered plasma frozen within ---(b)(4)--- after collection and recovered plasma frozen within ---(b)(4)--- after collection for the production of Wilate, we requested that the firm stipulates in the biologics license application that only U.S. recovered plasma under these two categories, and U.S. Source Plasma, will be used for the manufacture of Wilate lots to be distributed to the U.S. market. And, Octapharma agreed to this request.

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

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

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

[(b)(4)]

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) -----

Cryoprecipitate manufacture (see 3.2.P.3.4)

[(b)(4)]

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.

Product-related impurities (see 3.2.P.5.5)

[(b)(4)]

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

Comments: In response to our question on the claimed ratio of VWF:RCo to FVIII:C being 1, Octapharma now proposes a final drug product specification for this ratio to be --(b)(4)--, i.e., a range of --(b)(4)--, which represents roughly ± 1 standard deviation. The proposed specification is acceptable at this time. However, we recommend that Octapharma perform periodic evaluation when more information from the manufacturing process and the clinic are gathered.

VWF Parameters II (3.2.P.5.5)

[(b)(4)]

Comments: The ratios of these various parameters seem quite consistent amongst the conformance lots. However, the data from PK studies suggested that these parameters were affected differently *in vivo*. The reason could be due to the different rates of metabolism for different sizes of multimeric structure. Octapharma should address the lack of correlation between results in the above table and those observed in the PK studies.

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:

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

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

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

3.2.P: Drug Product

3.2.P.1 Description:

VWF lyophilized powder

Component	Quantity/vial		Function
VWF	450 IU	900 IU	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 Pharmaceutical Development:

3.2.P.2.1 Drug Substance 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	See Report under 3.2.P.2.7
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3.2.P.2.6 Compatibility-

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

- Octapharma informed the Agency that they will not use the ---- (b)(4) ---- device at this time.

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.

- - (b)(4) -

- - (b)(4) -

- - (b)(4) -

One page determined to be not releasable: (b)(4)

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

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

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

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

- -----(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

3.2.P.3.3: Manufacturing Summary- Report 150MOP18x/01/U

[(b)(4)]

Four pages determined to be not 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)-	-(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: $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, Glycine, Sucrose, NaCl, $\text{Na}_3\text{citrate} \cdot 2\text{H}_2\text{O}$

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). The following is an updated version in November 2009.

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)-
	---(b)(4)---	
Moisture	-(b)(4)-	-----(b)(4)----
FVIII activity	---(b)(4)---	Ph. Eur. (CS)
-(b)(4)-----	---(b)(4)---	
VWF R:Co	------(b)(4)-----	Ph. Eur. (R:Co)
VWF / FVIII	--(b)(4)--	
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). In response to our request for the procedures for establishment and maintenance of in-house VWF reference standards, Octapharma submitted standard operating procedure 006SOP019, and indicated that all versions of the

in-house standard and their verifications were tested on VWF:RCo activity according to the master SOP 130SOP056 against the primary standard first International Standard for VWF concentrate, NIBSC Code 00/514.

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)-----

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

- ------(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)

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

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

Octapharma provided report 6MS1030 on compatibility of the -(b)(4)- device with Wilate. The studies demonstrate compatibility of the device with Wilate and no adsorption of factor VIII and von Willebrand factor to the syringe and infusion set. Octapharma informed the Agency in 2009 that Wilate will not be packaged with the ---(b)(4)-- device.

(2) **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 <input type="checkbox"/> m filter	------(b)(4)-----
Filter Material	-(b)(4)-
Sterilization	------(b)(4)-----
Compatibility	------(b)(4)----- -----

Octapharma provided report 6MS1031 on compatibility of the Mix2Vial device with Wilate. The studies demonstrate compatibility of the device with Wilate and no adsorption of factor VIII and von Willebrand factor to the syringe and infusion set. The Mix2Vial device is currently used in several of U.S. licensed products, such as Monoclate-P, Humate-P and Kogenate FS.

Labeling: This was updated in November 2009.

- Prescribing Information: separate document with track changes
- Vial labels state shelf life, 36 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 36-month shelf life.
- 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. Octapharma has revised the carton to remove the 510(k) number.

In October 2007, we had some discussion on the proprietary name “Wilate”, and based on the following, I recommended that we allow Octapharma to use "Wilate" as the proprietary name for product under STN 125251:

- The "ate" at the end is for "eight" as in factor VIII. Since we have decided to allow Octapharma to use the proper name "von Willebrand factor/factor VIII complex (Human)", and label the product with both VWF:RCo and FVIII:C potencies, it would not be consistent to not allowing them to use a proprietary name that indicates the presence of factor VIII.

- There are exceptions: Talecris' antithrombin III is called Thrombate. ReFacto and the upcoming Xyntha are two names for Antihemophilic Factor (Recombinate) that do not end with "ate".

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

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

The recommendation was agreed upon by members of the review committee and Dr. Toby Silverman. APLB also found the proprietary name Wilate to be acceptable.

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

.

[
--(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) -----

Process Validation Objectives-

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

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

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

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

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

Octapharma - (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).

The supplier for polysorbate 80 for both Octapharma and ----- (b)(4) -----

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) -----	130SOP095	00VAL095
----- (b)(4) -----	130SOP062	00VAL062
Test for Sterility ----- (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- 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.

Information on stability was reviewed by Ms. Eleanor Koo and summarized in her review memo. She concluded that “Base on the presented stability studies, a shelf life of 24 months can be guaranteed under the storage condition at ----(b)(4)---- and protected from light.” for both the 450 IU/vial and 900 IU/vial dosage strength. The results also confirmed that reconstituted Wilate at both 450 IU/vial and 900 IU/vial are stable for -(b)(4)- in the beginning and at the end of the proposed shelf-life, i.e., 24 months -(b)(4)-.

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

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

3.2.P.3 Manufacture:

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

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

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

Octapharma provided the respective time and temperature limits used during each of the steps in their response to Question # 8, Amendment # 8.

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) -----

-(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)----
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
Determination of ----- (b)(4) -----	130SOP016	00VAL016
----- (b)(4) -----	130SOP039	00VAL039
----- (b)(4) -----	130SOP095	00VAL095
----- (b)(4) -----	130SOP108	00VAL108
-----	130SOP062	00VAL062
Test for Sterility by ----- (b)(4) -----	131SOP120	00VAL106
----- (b)(4) -----	130SOP089	

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)-----

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

Results

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

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) ---.

Results of testing of Conformance Lot

Don Lebel and Laura Wood assayed the six (6) conformance lots for VWF:RCo and FVIII:C activities, respectively.

The VWF:RCo and FVIII:C results are summarized as follows:

TEST DATE	Lot #	VWF:RCo Activity IU/mL	Assayed Results IU/mL	Vial mL Vol	% of Labeled Value	FVIII:C Labeled IU/mL	FVIII:C Assayed IU/mL	% of Labeled Value
10/19/2007	----- (b)(4) -----	90.0	41.37	5	46.0%	77.0	79.8	104%
10/19/2007	----- (b)(4) -----	90.0	38.77	5	43.1%	77.0	79.8	104%
10/19/2007	----- (b)(4) -----	90.0	70.39	5	78.2%	90.0	90.0	100%
10/19/2007	----- (b)(4) -----	90.0	65.79	10	73.1%	94.0	92.0	98%
10/19/2007	----- (b)(4) -----	91.0	69.15	10	76.0%	82.0	79.3	97%
10/19/2007	----- (b)(4) -----	84.1	62.09	5	73.8%	79.0	77.6	98%
10/19/2007	----- (b)(4) -----	84.1	64.50	10	76.7%	83.0	90.2	108%
10/26/2007	----- (b)(4) -----	90.0	56.67	5	63.0%	77.0	79.8	104%
10/26/2007	----- (b)(4) -----	90.0	64.83	5	72.0%	77.0	79.8	104%
10/26/2007	----- (b)(4) -----	90.0	69.75	5	77.5%	90.0	90.0	100%
10/26/2007	----- (b)(4) -----	90.0	71.02	10	78.9%	94.0	92.0	98%
10/26/2007	----- (b)(4) -----	91.0	77.01	10	84.6%	82.0	79.3	97%
10/26/2007	----- (b)(4) -----	84.1	63.81	5	75.9%	79.0	77.6	98%
10/26/2007	----- (b)(4) -----	84.1	69.73	10	82.9%	83.0	90.2	108%

The VWF:RCo activity values generated in CBER lab are consistently lower than the labeled value, and one lot did not meet our internal acceptance criterion of ± 30 % of labeled value. The percentage of label ranges from 43 to 85 %. The average of all the values is about 70 % of the label. So, the discrepancy in the VWF:RCo values generated by the two labs will likely result in some Wilate lots to not meeting our lot release criterion for VWF product. As indicated by Octapharma, they also observed a similar decrease in VWF:RCo results when Wilate was assayed with the automated method.

On the other hand, the results of FVIII:C potency as determined by a ----- (b)(4) ----- assay agree very well with the labeled potency. The percentage of label ranges from 97 to 108 %. This will also affect the new specification for the ratio of VWF:RCo/FVIII:C as proposed.

Comments: In Amendment # 24, Octapharma submitted information to support that the VWF:RCo assay they use is adequately validated. Don Lebel reviewed this data and found the assay to be acceptable. However, ----- (b)(4) ----- showed that the VWF in Wilate has multimers made up of only up to - (b)(4) - VWF molecules. Multimers of VWF in either plasma or Humate-P can have as many as - (b)(4) - VWF subunits. This difference could explain the behavior of Wilate in the automated VWF:RCo assay and the PK study. In addition to the questions posed by Ifethkar

Mahmood, another question would be: Can a product -----(b)(4)----- multimers be efficacious in the indications intended?

From a survey conducted by the North America Specialized Coagulation Laboratory Association in 2004, for Ristocetin cofactor activity, 51% of the labs surveyed use aggregometry, 42% use automated method and 6% use ELISA. The trend is most likely moving towards using an automated method. As a result, this will pose a problem for lot release and testing by other clinical labs when VWF:RCo values are consistently 20-30% below those on the label.

RECOMMENDATION

Discrepancies in the VWF:RCo potency values derived from the manual and automated method remains unresolved at this time. This could be attributed to the nature of the VWF molecule in this product. Similarly, the VWF:RCo values in patient plasma in the PK studies were deemed not interpretable. Together with other issues related to the clinical studies, the review committee recommends that a CR letter be issued to Octapharma describing the deficiencies as follows:

1. Please establish as a release specification the ratio of VWF:RCo to Factor VIII clotting activity, and propose an acceptance criterion based on your manufacturing and clinical experiences. The proposed ratio of ---(b)(4)-- IU/IU ratio is acceptable at this time but should be re-evaluated annually and preferably tightened as more information is available.
2. Regarding the determination of residual moisture in the final drug product,
 - a. The specification for inter-method correlation of -(b)(4)- does not reflect your experience in practice with $r = 0.98$. Please comment.
 - b. It is noted that in the calibration, results from 13 spectra were rejected as outliers out of -(b)(4)- spectra obtained from -(b)(4)- samples. Please describe the criteria for outlier rejection.
 - c. Please support the correlation between the ----(b)(4)---- and -----(b)(4)----- procedures by more extensive testing of different samples (vials) from the same lot by the two techniques. Precision by each technique would include vial-to-vial variability, but would provide information as to the relative accuracy of each technique in establishing a value for residual moisture content for a given lot.
 - d. The -(b)(4)- determination of water in a solid must be calibrated with reference to the -(b)(4)- procedure. Please establish the -(b)(4)- procedure as the “reference” or official regulatory method, and the -(b)(4)- method as an “alternate” method for routine lot release.

3. Since Octapharma currently uses recovered plasma frozen within ---(b)(4)-- after collection and recovered plasma frozen within ----(b)(4)-- after collection for the production of Wilate, please stipulate in the biologics license application that only U.S. recovered plasma under these two categories, and U.S. Source Plasma, will be used for the manufacture of Wilate lots to be distributed to the U.S. market.
4. You indicated in your amendment that potency value of Wilate generated using an automated VWF:RCo assay method is lower than that derived using a manual assay method. In a survey conducted by the North American Specialized Coagulation Laboratory Association in 2004, 51 % of laboratories use aggregometry to determine VWF:RCo activity, while 42 % use an automated method and 6 % use an ELISA method. The trend is likely to be moving towards automation.
 - a. Please describe how you would address the discrepancies in VWF:RCo values derived from the different methods when physicians will depend on VWF:RCo values generated from clinical labs, which may be different from the labeled values, for dosing.
 - b. Similarly, we obtained VWF:RCo values that were lower than the labeled potency when conformance lots were assayed in our lab using an automated method. Please propose a plan to reconcile such differences to minimize failure of Wilate batches through the lot release program.
5. Under section 3.2.P.5.5, the ratio between the various VWF parameters, VWF:Ag, VWF:RCo, and VWF:CB of the conformance lots is quite consistent and close to 1. However, in the pharmacokinetics (PK) studies, these ratios did not follow a particular pattern, and were far away from 1. For example, the PK profile following VWF:RCo is different from that followed by VWF:Ag indicating that these parameters were affected differently *in vivo*. Please comment with reference to the structure of the VWF molecule in Wilate.
6. Please provide data to demonstrate that -(b)(4)- 0.1% polysorbate 80 solvent at the end of expiry when reconstituted with Wilate final drug product results in a reconstituted product that meets specification.
7. Please provide updated stability data in your response to this action letter.
8. Please provide an updated development report as the one enclosed under 3.2.P.2.7 regarding Pharmaceutical Development.

The above 8 items were conveyed to Octapharma in the CR letter dated 8 January 2008.

Review of Octapharma's responses to the CMC issues in the CR letter:

Octapharma responded to the CR letter in an amendment dated 3 June 2009. In addition, there are multiple amendments to the BLA in response to our information request. Their responses and our comments are summarized as follows:

- In the amendment dated 3 June 2009, Octapharma provided a revised version of the Final Product Specification for Wilate in which a ratio for VWF/FVIII of --(b)(4)-- (IU/IU) was included. On 30 November 2009, Octapharma updated the content of the active ingredients as 450 (900) IU VWF:RCo and 450 (900) IU FVIII, they revised the VWF/ FVIII ratio to be -----(b)(4)----- . This represents roughly ± 1 standard deviation. The proposed specification is acceptable at this time. However, we recommend that Octapharma perform periodic evaluation of this parameter when more information from the manufacturing process and the clinic are gathered.
- Regarding the determination of residual moisture in the final drug product, Octapharma has re-evaluated some of the validation parameters, and correlation between the -----(b)(4)---- and -----(b)(4)----- methods. More, importantly, Octapharma stated that “The -----(b)(4)--- procedure is established as the “reference” or official regulatory method, and the -(b)(4)- method as an “alternate” method for routine lot release. So, the response is acceptable.
- Regarding the condition under which recovered plasma is collected that is used for the manufacture of Wilate, “Octapharma confirms that only U.S. plasma frozen within --(b)(4)--- after collection and U.S. Source Plasma will be used for the manufacture of Wilate lots to be distributed to the U.S. market.” The response is acceptable.
- Regarding the issues related to the different methodologies used to determine VWF:RCo activity, please refer to the review memo by Mr. Don Lebel for details. In summary:

In an attempt to improve the sensitivity of the VWF:RCo assay, Octapharma, in collaboration with -----(b)(4)-----, developed a method based on the Behring Coagulation System (BCS). The system was later renamed due to a change in ownership of the company, but the abbreviation stands as the BCS assay. In addition to acquiring this automatic method, Octapharma also modified the assay condition, most notably -----(b)(4)----- . While the sensitivity was increased to allow its determination of low concentrations of VWF:RCo activity in patient plasma in the PK study. The values as compared to those derived from the standard BCS method and the assay used in CBER lab have always found to be at least 10% higher, as illustrated in the table below.

Comparison of VWF:RCo values determined by Different Methods

Wilate Lot	Manual Assay IU/mL	Std BCS IU/mL (% manu.)	Modified BCS IU/mL (% manu.)
Lot 1	84	72 (86)	92 (109)

Lot 2	84	43 (51)	61 (73)
Lot 3	78	65 (83)	80 (103)
Lot 4	84	58 (69)	83 (99)
Lot 5	78	52 (67)	89 (114)
Lot 6	78	56 (72)	84 (108)

In anticipation of problems in lot release testing and discrepancy with other laboratories where the modified BCS assay is not commonly used, we recommended Octapharma to use either the manual or standard BCS method for potency assignment of the Wilate product. In a November 2009 communication with the Agency, Octapharma has agreed to use the manual assay method to label the Wilate product. The response is acceptable.

- Regarding the stability of Wilate reconstituted with (b)(4)- 0.1% polysorbate 80 diluent at the end of its dating period, Octapharma provided a study report that presented data to demonstrate that Wilate reconstituted with aged diluent resulted in a product that met all release specifications.

For all tested parameters including VWF:RCo and FVIII activities, the results for Wilate 450 IU, batch no. ---(b)(4)----, reconstituted with (b)(4)- months old (lot no. (b)(4)-) and (b)(4)- months old (lot no. (b)(4)-) diluent, met all release specifications. Also, for Wilate 900 IU, batch no. (b)(4)-, reconstituted with (b)(4)- months old (lot no. (b)(4)-) and (b)(4)- months old (lot no. (b)(4)-) diluent, the results are also within the range of the release specifications.

Therefore, the results demonstrate that the reconstitution of Wilate with (b)(4)- 0.1 % polysorbate 80 diluent at the end of its dating period does not have any adverse effects on the quality of the final product. The response is acceptable

- Regarding updated stability results:

In their response to the CR letter dated 3 June 2009, Octapharma provided updated results from stability studies. The results include 24 months' data for Wilate 450 IU and 900 IU stored at long-term conditions ($+5 \pm 3^{\circ}\text{C}$ and -----(b)(4)-----), 6 months for the accelerated (----- (b)(4)-----) studies. Reconstitution data were collected at the initial time point and after -----(b)(4)----. Temperature excursion studies are also performed evaluating the effect of short-term excursions outside the labeled storage conditions. In this case, the samples are stored at -----(b)(4)-----.

After a total storage period of 36 months, all samples will be tested for all parameters included in the regular study program.

For Long-Term Studies, Wilate 450 IU and 900 IU are stable at $+5^{\circ}\text{C}$ for up to 24 months. At $+25^{\circ}\text{C}$, one batch (-----(b)(4)----) shows borderline results for Factor VIII after -----(b)(4)----- . After (b)(4)- months, the values are again within the specification limits as well as all other tested attributes. Furthermore, no remarkable

changes could be noticed by -----(b)(4)-----
distribution in comparison to the initial time point. The result could be attributed to the low initial content of Factor VIII and the variance of the assay.

For the accelerated condition studies at -----(b)(4)-----, 6 months' data are provided for both fill sizes. For two batches (----- (b)(4)-----), the Factor VIII activity is below the limit of specification. All other tested attributes are compliant with the relevant specification and demonstrate the stability of the product. --(b)(4)--
----- distribution did not show remarkable changes compared to the initial testing. Therefore, the exposure to elevated temperature and humidity is covered for at least 3 months. According to the stability study design data for the temperature excursion studies will be presented after 36 months.

In addition to the evaluation of the stability of the final drug product under various storage conditions, Octapharma also presented results to support the stability of cryoprecipitate and the diluent (0.1% polysorbate 80 in WFI) manufactured at two facilities. Based on the stability results, Octapharma proposed the following shelf-Life:

- Wilate may be stored for 36 months at +2°C to +8°C (36°F to 46°F) protected from light from the date of manufacture. Within this period, Wilate may be stored for a period of up to 6 months at room temperature (maximum of +25°C or 77°F). The starting date of room temperature storage should be clearly recorded on the product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature, or the expiration date on the product vial, whichever is earliest. Wilate should not be freeze.
- The diluent (0.1% polysorbate 80 in WFI) may be stored for -----(b)(4)-----

-----, The diluent may be stored at any time 6 months at room temperature (not to exceed +25°C/77°F), the shelf-life expires after the storage at room temperature.
- Since the manufacture process of Wilate is a continuous process starting from cryoprecipitate all the way to the final product, there is no long term storage for the bulk drug substance. Octapharma has established a shelf-life of -(b)(4)- for the cryoprecipitate when stored at temperature not to exceed -(b)(4)-. The cryoprecipitate is also stable if transported at -----(b)(4)----- during the storage period.

The proposed dating periods for the final drug product and diluent are acceptable.

- Regarding further development since BLA submission, Octapharma stated that “No further development has been incorporated since 2006.” The response is acceptable.

RECOMMENDATION

Information submitted in Octapharma's response to the CR letter dated 3 June 2009, and subsequent amendments satisfactorily addressed all the CMC issues in the CR letter. Therefore, this BLA can be approved from a CMC perspective.