

MEMORANDUM

Date: 30 August 2007

From: Eleanor Koo, HFM-340

To: Nancy Kirschbaum, Ph. D (Scientific Leader-HFM 392)

Subject: Review of Stability Information in Octapharma's BLA for von Willebrand Factor/Coagulation Factor VIII Complex (Human) [Wilate]

CC: Timothy Lee, Ph.D., Acting Lab Chief (HFM-392)
Laboratory of Hemostasis/ DH/OBRR

Franklin Stephenson, RPM (HFM-380)

Overview:

Octapharma has submitted a Biologic License Application for WILATE (Human coagulation factor VIII (FVIII) and human von Willebrand factor (VWF). This application has been formatted in accordance with the FDA's "Guidance for Industry: Submitting Marketing Applications According to the ICH-CTD Format-General Considerations", August 2001 and FDA's Manual of Standard Operating Procedures and Policies- General Information, SOPP 8007, "DCC Binding Procedures for Regulatory Documents", November 1999.

WILATE is supplied as a powder for reconstitution and intravenous injection. The medicinal product contains per vial 450 IU /900 IU FVIII: C and -----(b)(4)----- VWF: RCo and will be reconstituted with the supplied Solvent: 5 mL/10 mL Water for Injections with 0.1% Polysorbate 80.

WILAE is indicated in adult and pediatric patients for the treatment -----(b)(4)----- of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease (VWF), and in mild and moderate VWD where use of DDAVP (1-deamino-8-D-arginine vasopressin/desmopressin) treatment is ineffective or contra-indicated. -----(b)(4)-----
-----.

WILATE introduces a unique combination of product characteristics and represents a new product generation for the treatment of VWD.

WILATE has a double virus inactivation step in its manufacturing process and high purity product characteristics for the treatment of VWD Patients. Moreover, WILATE contains both functional VWF and FVIII in physiological amounts with similar and physiological

pharmacokinetic properties. The availability of WILATE will help secure the supply of VWF-concentrates also in the future, when the number of diagnosed and prophylactically-treated VWD patients will increase.

WILATE is manufactured at OCTAPHARMA Pharmazeutika Produktionsgesm.b.h., 235 Oberlaaer Strasse, and A-1100 Vienna, Austria. This facility has recently been inspected by CBER on 16-20 January 2006 in the coursed of a GMP inspection for our Immune Globulin Intravenous, Octogam 5% STN 125062, and on 22-31 March 2006 in the coursed of a pre-license inspection for our Human Albumin 5% and 25%, STN 125154. The site for WILATE is ready for a Pre-Approval inspection.

On 29 June 2007 Octopharma submitted to FDA an “Amendment #009-Information about course of Event”- Six months stability data (Wilate (vonWillebrand Factor/Factor VIII Concentrate (Human)-STN: 125251/0).

An event which has taken place at our facility in Vienna and which affected the stability study 06P014 on BLA conformance batches at six (6) months test time point.

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

Corrective and Prevent Actives:

Immediately after detection of the accident, the Maintenance Department was informed, appropriate technical repair works have been executed and the specified room temperature was met again at noon of April 10, 2007. A deviation report according to 015SOP010” deviation management” was initiated. On the same day the faulty compressor was replaced and an alarm system integrated in the temperature recorder (was initiated) and tested for proper performance.

As additional corrective action, since the occurrence of the event all alarm systems for stability chambers have been reconstructed in that to have now -(b)(4)- independent systems guaranteeing an alarm to maintenance department as well as the system owner to initiate immediate actions.

The above incident had an impact on the following stability project:

- Willate 450/900 IU Study 06P014 stability study on BLA conformance batches at 6 months test time point.

The product was exposed to the elevated temperature for up to 82 hours. The 6 months test results (Wilate 450/900 IU.: 000SSR181.06P014.01/USA, stability study on BLA conformance batches) did not demonstrate any quality impact at the proposed storage condition 2-8C as well as at 25C. Consequently, the stability study will continue.

A final stability study report with 36 months data for European batches (Wilate 900 IU.: 00SSR181.03P007.10/international) as amendment # 009 to Wilate BLA (ATN: 125251/0) also submitted and results are within specification.

Review Stability data:

WILATE is a human, plasma-derived, high-purity, double virus inactivated coagulation factor concentrate containing factor VIII (FVIII) and von Willebrand factor (VWF). The very gentle manufacturing process developed for this product allows co-harvesting of native FVIII and VWF utilizing the favorable properties of a -----(b)(4)----- . The production of WILATE ensures a high degree of reproducibility and the molecular integrity and function of FVIII and VWF is maintained. Wilate contains a very small amount of accompanying proteins, which, in addition, constitute the natural environment of the FVIII/VWF complex, and the specific activity of the product is very high (≥ 60 IU FVIII:C/mg total protein). VWF is the natural stabilizer of FVIII and, thus, no human serum albumin is added to WILATE.

The product is available in two potencies, namely in 450 IU and 900 IU FVIII/vial.

Stability study reports for WILATE 450 IU (000SSR181. 03P003.06/international) comprising 36 months and for WILATE 900 IU ((000SSR181. 03P007.09/international) comprising 24 months, are submitted to support the claimed shelf life of 24 months at 2°C to 8°C (36°F to 46°F) from the date of manufacture and protected from light. Within this period Wilate may be stored at any time 6 months at room temperature (Maximum 25°C/77°F); the shelf life expires after the storage at room temperature (Maximum 25°C/77°F).

The stability data are based on batches produced for the European markets and used to support Marketing Authorizations of WILATE within the EU.

Review Final Drug Product stability:

Stability study design (000SSD181.06P014.00/USA) is provided. The design defines a full stability study on Wilate 450 IU and 900 IU according to the current guidelines for stability testing (ICH Q1A (R2) Stability Testing Guidelines: Stability Testing of New Drug Substances and Biotechnological/Biological Products; ICH Q1D, Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products).

In addition to the full stability study a temperature excursion study is performed to cover short term exposures to elevated temperatures during shipment.

The storage conditions are as following: Samples are stored at OCTAPHAEMA GmbH, Vienna, Austria.

1. $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$; $-(b)(4) \pm 2^{\circ}\text{C}$ ----(b)(4)---- at dark and upright. The sterility will be tested at 0, 24, 36 and $-(b)(4)$ - months intervals. These studies end at $-(b)(4)$ - months.
2. Accelerated stability study: Samples stored at -----(b)(4)----- at dark and upright, and the sterility will be tested at 0 and 6 months.
3. Temperature excursion study: The study is performed with samples of all batches used in the regular study program. -----(b)(4)-----

Packaging: The same packaging material is used for marketing of the product are used for the stability studies.

Primary packaging: 20 ml glass vial (type 1), lyophilization stopper 20mm.

Secondary packaging: The stability batches are labeled with labels of the same type and size as the standard labels. The outer carton is also made of the same material and size as the standard cartons.

Long-term stability study for final drug product (with ----(b)(4)----- stoppers): All samples are stored at OCTAPHARMA GmbH, Vienna, Austria.

Stability study report for 450 IU 000SSR181.03P003.06 /International (comprising 36 months)

The stability study report comprised (----- (b)(4) -----)

- 36 months data of long term studies at 5 C and ----(b)(4)-----
- 12 months data of intermediate studies at ----(b)(4)-----
- 6 months data of accelerated studies at ----(b)(4)-----

Lot #	Storage Condition	Start of study	Data available Month	Status
----(b)(4)----	5C, dark, upright	03 December 2003	36	Completed
	25C/--(b)(4)--, dark, upright		-(b)(4)-	Completed
	----(b)(4)----, dark, upright		12	Completed
	----(b)(4)----,		6	Completed

	dark, upright			
----- (b)(4) -----	5C, dark, upright	03 December 2003	36	Completed
	25C/--- (b)(4) ---, dark, upright		--- (b)(4) ---	Completed
	---- (b)(4) ----, dark, upright		12	Completed
	---- (b)(4) ----, dark, upright		6	Completed
----- (b)(4) -----	5C, dark, upright	03 December 2003	36	Completed
	25C/--- (b)(4) ---, dark, upright		--- (b)(4) ---	Completed
	---- (b)(4) ----, dark, upright		12	Completed
	---- (b)(4) ----, dark, upright		6	Completed

Statistical Evaluation for stability data:

Wilate 450 IU/vial: Stability data of the long-term studies for the Factor VIII activity have been statistically evaluated by linear regression with two-sided 95-percent confidence limits. Results for the Ristocetin cofactor activity are depicted in scatter graphs without statistics since linear regression does not apply to quantal data.

All real-time data comprised in the stability study report at hand suggest the stability of Wilate 450 IU throughout the scheduled period: 6 months at accelerated (----- (b)(4) ----), 12 months at intermediate condition (---- (b)(4) ----), and 36 months at long-term studies (5°C, ----- (b)(4) ----). The stability of the product at elevated temperature is proved and a shelf-life up to 36 months guaranteed when store at 5°C --- (b)(4) --- and protected from light.

All test attributes including potency parameters Factor VIII and Ristocetin cofactor activity support the stability of the product.

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Comments:

Base on the presented stability studies a shelf life of 24 months can be guaranteed under the storage condition at 2C --- (b)(4) --- and protected from light.

Please consult a statistician for statistical evaluation of stability data.

Stability study report for 900 IU 000SSR181.03P007.09 /International (comprising 24 months)

The stability study report comprised (------(b)(4)-----)

- 24 months data of long term studies at 5 C and -----(b)(4)----
- 12 months data of intermediate studies at ----(b)(4)---
- 6 months data of accelerated studies at ----(b)(4)-----

Lot #	Storage condition	Start of study	Data available Month	Status
------(b)(4)-----	5C, dark, upright	30 July 2003	24	ongoing
	25C/--(b)(4)--, dark, upright		-(b)(4)-	ongoing
	----(b)(4)----, dark, upright		12	completed
	----(b)(4)----, dark, upright		6	completed
------(b)(4)-----	5C, dark, upright	30 July 2003	24	ongoing
	25C/--(b)(4)--, dark, upright		-(b)(4)-	ongoing
	----(b)(4)----, dark, upright		12	completed
	----(b)(4)----, dark, upright		6	completed
------(b)(4)-----	5C, dark, upright	17 December 2003	24	ongoing
	25C/--(b)(4)--, dark, upright		-(b)(4)-	ongoing
	----(b)(4)----, dark, upright		12	completed
	----(b)(4)----, dark, upright		6	completed

On 29 June 2007, the firm submitted a final stability study report with 36 months data for European batches (Wilate 900 IU.: 00SSR181.03P007.10/international) as amendment # 009 to Wilate BLA (lots -----(b)(4)-----) (ATN: 125251/0) was also submitted and all results are within specification.

Statistical Evaluation for stability data:

Wilate 900 IU/vial: Stability data of the long-term studies for the Factor VIII activity have been statistically evaluated according to ICH Guideline Q1E. In particular, analysis of covariance (ANCOV A) is applied for a quantitative attribute with a proposed acceptance criterion to test for differences in slopes and intercepts of the regression lines. These tests are performed on a significance level of 0.25 (p-value).

Assay data for Ristocetin cofactor activity are depicted in scatter graphs without statistics since linear regression does not appropriate to apply to quantal data.

All real-time data comprised in the stability study report at hand suggest the stability of Wilate 900 IU throughout the scheduled period: 6 months at accelerated (-----)(b)(4)-----), 12 months at intermediate condition (-----)(b)(4)-----), and 24 months at long-term studies (5°C, ---)(b)(4)--- ----). The stability of the product at elevated temperature is proved and a shelf-life up to 36 months guaranteed when store at 5°C -(b)(4)- and protected from light.

All test attributes including potency parameters Factor VIII and Ristocetin cofactor activity support the stability of the product.

Comments:

Base on the presented stability studies a shelf life of 24 months can be guaranteed under the storage condition at 2C -(b)(4)- and protected from light.
Please consult a statistician for statistical evaluation of stability data.

Batches produced in 2006 for stability studies- used for US BLA

Batches produced in 2006 for stability studies- used for US BLA

Batch	Potency	Manufacturing date
-----)(b)(4)-----	450 IU	08/2006
-----)(b)(4)-----	450IU	08/2006
-----)(b)(4)-----	900 IU	09/2006
-----)(b)(4)-----	900 IU	09/2006
-----)(b)(4)-----	450 IU	09/2006
-----)(b)(4)-----	900 IU	09/2006

There are no long term stability studies data provided for batches of WILATE 450 IU and 900 IU use for US BLA. The long term stability studies for these were initiated in November 2006.

Comment:

1. Please provide at least 6 months stability data of the 450 IU and 900IU of the batches produced in 2006 for stability studies used for US BLA, as soon as they become available.(was provided on 29 June 2007, see P13)
2. Please advise that these lots (used for U S BLA) have the identical container/closure system as lots -----(b)(4)-----
----- (international).

Comparison of the manufacturing process: Between 2002/03 and today (August/September, 2006) some modification with regard to the manufacturing process have been implemented.

Batch numbers and date of production for the concerned batches are listed below:

Batches produced in 2002/03 for stability studies- used for EU registration

Batch	Potency	Manufacturing date
-----(b)(4)-----	450 IU	11/2002
-----(b)(4)-----	450IU	12/2002
-----(b)(4)-----	450 IU	12/2002
-----(b)(4)-----	900 IU	05/2003
-----(b)(4)-----	900 IU	06/2003
-----(b)(4)-----	900 IU	10/2003

Batches produced in 2006 for stability studies- used for US BLA

Batch	Potency	Manufacturing date
-----(b)(4)-----	450 IU	08/2006
-----(b)(4)-----	450IU	08/2006
-----(b)(4)-----	900 IU	09/2006
-----(b)(4)-----	900 IU	09/2006
-----(b)(4)-----	450 IU	09/2006
-----(b)(4)-----	900 IU	09/2006

The previous “Method of preparation (MOP)” for EU registration and the submitted US MOP were compared. All modifications in the MOP, in particular all process relevant parameters that differ with respect to their approved ranges are provided for review.

It is of importance to note that all modifications in the batch records are within the ranges specified by both the previous and submitted MOPs.

Comment: *Defer comment of the manufacturing process modifications to the manufacturing process reviewer.*

Stability data for final drug product (Reconstitution):

The stability of the reconstituted product Wilate at room temperature was investigated. Samples were reconstituted as described in the user's information to a final concentration of nominal 90 IU FVIII/mL using WFI containing 0.1 % Polysorbate 80 as the solvent. Both FVIII: C and VWF: RCo being the biologically active compounds of Wilate were tested at the different pre-scheduled time points.

Final containers from three batches of each filling size, i.e. 450 and 900 IU FVIII/vial were investigated. In order to allow direct comparison of results and to reduce a possible impact of sample manipulation on test results (e.g. freezing. thawing) all 6 batches were investigated in sampling at predefined time points (e. after 0, -----(b)(4)-----).

The 450 and 900 IU freeze dried samples were reconstituted with 5 ml and 10 ml solvent (WFI containing 0.1% Polysorbate 80) respectively to reach a final concentration of nominal 90 IU FVIII/ml. Both the lyophilized product and the solvent were allowed to reach room temperature before starting the reconstitution and subsequent experiment. Samples were drawn after different pre-scheduled time points (----- (b)(4) -----) and analyzed.

Investigated Batches of WILATE for 450 IU FVIII/vial after reconstitution and storage in final container (April 2005)

Batch #	Potency IU/vial	FVII:C IU/ml	VWF:RCo IU/ml	Time Point (hour)
-----(b)(4)----	450	109	78	0
-----(b)(4)----	450	108	78	0
-----(b)(4)----	450	93	71	0
-----(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)-	-(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)----	-(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)-	-(b)(4)-
-----(b)(4)----	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
-----(b)(4)----	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-

Evaluation of the results:

Determination of FVIII activity (FVII: C) and VWF: Ristocetin Cofactor (VWF: RCo) were performed according to SOPs (000SOP263; slope ratio model and 000SOP056 respectively). For the determination of FVIII: C and VWF: RCo three independent dilutions were analyzed, each in duplicate. The graphical evaluation showed that the FVIII: C and VWF: RCo values including the upper and lower FVIII: C limit and VWF: RCo as specified, i.e. ---(b)(4)-- FVIII/ml and -(b)(4)- respectively. The trend of FVIII:C over time is provided. Data represent the mean values of the three individual batches at the corresponding time point.

Comments: All samples were within the specified FVIII: C potency of ----(b)(4)---- and WF: RCo potency of ----(b)(4)---- for ----(b)(4)-----.

Investigated Batches of WILATE for 450 IU FVIII/vial reconstitution after stored --(b)(4)-- ----- at 25° C in final container (March 2006)

Batch #	Potency IU/vial	FVII:C IU/ml	VWF:RCo Mean Value ⁸² (IU/ml) ⁸⁰	Time Point (hour)
----(b)(4)----	450	79	70	0
----(b)(4)----	450	84	84	0
----(b)(4)----	450	92	84	0
----(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)-	-(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)----	-(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)-	-(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)-	-(b)(4)-	-(b)(4)-	-(b)(4)-

Investigated Batches of WILATE for 900 IU FVIII/vial reconstitution after stored -(b)(4)- ----- at 25° C in final container (March 2006)

with the FPS for this period of time. In order to see the principal trend of FVIII: C and VWF: RCo during storage of the reconstituted product the results were also presented as graphs.

Comment:

The results also conformed that reconstituted WILATE both 450 IU and 900 IU /vial potencies were stable for -----(b)(4)----- both in the beginning of and after the end of proposed shelf life, i.e. -----(b)(4)-----.

Post-Approval stability protocol and stability commitment:

Long term stability studies for WILATE 450 IU and 900 IU were initiated in November 2006. The conformance lots used for these stability studies have been produced with US plasma only.

Comment:

Please specify which US plasma was used to produced the conformance lots used for US BLA; recover plasma/source plasma?

The stability study protocol of WILATE 450/900 IU, study 06P014 is provided and reviewed.

The design defines a full stability study on WILATE 450 IU and 900 IU according to the current guidelines for stability testing ICH Q1A (R2) Stability Testing Guidelines: Stability Testing of New Drug Substances and Products; ICH Topic Q5C, Quality of Biotechnological Products: Stability testing of Biotechnological/biological Products; ICH Q1D, Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Product.

These long-term studies end after -(b)(4)- months. Sterility will test at 0, 24, 36 and -(b)(4)- months at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and -(b)(4)- at dark and upright. The accelerated stability study will end after 6 months under the storage condition at -----(b)(4)-----. Sterility will test at 0 and 6 months.

In addition to the full stability study a temperature excursion study is performed to cover short-term exposures to elevated temperatures during shipment.

The stability after reconstitution will be tested after 0. -----(b)(4)----- at time points 0 and - --(b)(4)---.

Octapharma commits to report the results from the on-going stability study on a regular basis.

Comments:

1. There is no US BLA submission lots stability data provided, please submit at least six (6) months of stability data for US BLA lots, as soon as they become available.

Responses:

On 29 June 2007 Octopharma submitted to FDA an “Amendment #009-Information about course of Event”- Six months stability data (Wilate (vonWillebrand Factor/Factor VIII Concentrate (Human)-STN: 125251/0).

An event which has taken place at our facility in Vienna and which affected the stability study 06P014 on BLA conformance batches at six (6) months test time point.

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

Corrective and Prevent Actives:

Immediately after detection of the accident, the Maintenance Department was informed, appropriate technical repair works have been executed and the specified room temperature was met again at noon of April 10, 2007. A deviation report according to 015SOP010” deviation management” was initiated. On the same day the faulty compressor was replaced and an alarm system integrated in the temperature recorder (was initiated) and tested for proper performance.

As additional corrective action, since the occurrence of the event all alarm systems for stability chambers have been reconstructed in that to have now -(b)(4)- independent systems guaranteeing an alarm to maintenance department as well as the system owner to initiate immediate actions.

The above incident had an impact on the following stability project:

- Willate 450/900 IU Study 06P014 stability study on BLA conformance batches at 6 months test time point.

The product was exposed to the elevated temperature for up to 82 hours.

The 6 months test results for Wilate 450/900 IU.: 000SSR181.06P014.01/USA, stability study on BLA conformance batches (------(b)(4)----- for 450IU and lots -----(b)(4)----- of 900 I U) did not demonstrate any quality impact at the proposed storage condition 2-8C as well as at 25C.

All the test results are within specification limit. Consequently, the stability study will continue.

2. Please specify which US plasma was used to produced the conformance lots used for US BLA; recover plasma/source plasma?
3. Please consult a statistician for statistical evaluation of stability data.

Recommendation:

This submission is approvable

On 3 June 2009, Octapharma submitted additional stability results in their response to the CR letter. Please refer to the final memo of Tim Lee on the review of this stability information.