



Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

To: File **(STN)**

Company: Octapharma Pharmazeutika
Product: Coagulation Factor VIII/von Willebrand Factor Complex (Human)
Wilate

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Subject: **Coagulation Factor VIII/von Willebrand Factor Complex (Human)**
Lot Release / Conformance Testing
Final Review Memo

Summary

Coagulation Factor VIII/von Willebrand Factor Complex (Human), Wilate, is designated for the -----(b)(4)---- treatment of spontaneous and trauma induced bleeding episodes -----(b)(4)-----
-----in severe von Willebrand disease (vWD), and in mild and moderate vWD where use of 1-Desamino-8d-Arginine Vasopressin (DDAVP) treatment is ineffective or contraindicated.

The purpose of this review is to summarize and evaluate the Chemistry and Manufacturing (CMC), test method validation and testing methodology as well as the Standard Operating Procedure (SOP) used to determine vWF:Rcof Activity Assay potency for the Coagulation Factor VIII/von Willebrand Factor Complex (Human), product, trade name, Wilate.

The original Blood License Application (BLA) submission was received on December 13, 2006. A Complete Response Letter was forwarded to the company on January 8, 2008. A response was received from Octapharma on June 3, 2008.

A total of six (6) conformance lots were received as a part of the original submission.
FDA test results are included below:

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

SOP & Methods Validation

The test method utilized for determination of the vWF: Rcof Activity Assay, as submitted in the original BLA (Biologics License Application), was a manual (b)(4) method. This methodology is an approved method for vWF potency determination in European Union. The vWF: Rcof Activity Assay was carried out for semi-quantitative determinations by -----(b)(4)-----.

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

The manual (b)(4) method for determination of vWF Activity is a well established assay and is frequently utilized in clinical laboratories for vWF potency determinations both in Europe and the United States.

The manual (b)(4) methodology became problematic for this submission. The assay is a (b)(4) assay. A (b)(4) - assay gives potency results in distinct dilution factors with no intermediate potency values possible between the set dilutions used in the assay, giving step like results to the potency test results. Results are limited to one discreet series of possible concentrations 1%, 6%, 12%, 24% and 36% etc.

These step like results were determined to be not interpretable by the FDA Clinical Review Branch when reviewing PK studies for the determination of dosage strengths. The FDA recommended that Octapharma develop or investigate a more sensitive analytical method to measure relevant concentrations of vWF in Wilate samples and then conduct a PK study of Wilate utilizing a suitable sample size.

The manual (b)(4) methodology is an acceptable methodology for the determination of product potency for the purpose of assigning accurate labeled vial potency.

Conformance Lots/ Test Results (Original BLA Submission) Manual Methodology

As part of this review conformance lots were tested at the FDA testing laboratory using potency values established utilizing the Manual (b)(4) methodology. Acceptable range criterion for Lot Release testing is (b)(4) of the assigned labeled potency. Testing date 10/26/07. All lots passed Lot Release testing criterion.

<u>Lot No.</u>	<u>Labeled Value</u> <u>IU/mL</u>	<u>Assayed Values</u> <u>IU/mL</u>	<u>% of</u> <u>Labeled Value</u>
----(b)(4)----	90.0	64.8	72.0
----(b)(4)----	90.0	69.8	77.5
----(b)(4)----	90.0	71.0	78.9
----(b)(4)----	91.0	77.0	84.6
----(b)(4)----	84.0	63.8	75.9
----(b)(4)----	84.0	69.7	82.9

Lot release Potency testing was also performed utilizing the assigned potency values determined by the Original BCS (Siemens) (un-modified) assay methodology. Testing results are as follows: (acceptable range = (b)(4) of labeled value)

<u>Lot No.</u>	<u>Labeled Value</u> <u>IU/mL</u>	<u>Assayed Values</u> <u>IU/mL</u>	<u>% of</u> <u>Labeled Value</u>
----(b)(4)----	78.0	84.5	108.3
----(b)(4)----	75.0	78.8	105.1
----(b)(4)----	68.0	52.7	77.6

Lot Release and Conformance testing results are acceptable.

Discipline Review

FDA Complete Response Letter (CR) Dated January 8, 2008

The FDA submitted a Complete Response Letter to the Sponsor. The following is a CMC question relating to the vWF Assay. Other non-CMC questions were also submitted, by the review committee, and are not included in this review.

Question #31: You have indicated in your amendment submitted on November 13, 2007 that potency values of Wilate lots generated using an automated vWF: Rcof assay methods are lower than those 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: Rcof 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: Rcof values derived from different methods when physicians will depend on vWF: Rcof values generated from clinical laboratories.
- b. We obtained vWF: Rcof values that were lower than the labeled potency values when conformance lots were assayed in our laboratory using an automated method. Please propose a plan to reconcile such differences to minimize failure of Wilate batches through the lot release program.

Company Response to Question #31

In testing in our QC and research labs in Vienna and in collaboration with -----(b)(4)-----, we have found discrepancies in the values derived from a number of products including Wilate and including the WHO plasma and concentrate standard (Enclosure 17; pages 5, 7, 9). These discrepancies seem to be methodology dependent. As can be seen in the current re-analysis of the PK data from the WIL-12 crossover PK study (Enclosure 4), even within the same methodological system variations in the details of the method can make large differences in the results.

The data from ----(b)(4)---- laboratory "*The Ristocetin Cofactor Activity Assay, Automation, Harmonization and Validation*" (submitted as part of the Company Response to CR-letter dated January 8, 2008, Enclosure #7), indicates that the standard method proposed by the manufacturer of the instrument is not optimal for potency as well as plasma vWF: Rcof determinations and a modification of the methods are needed. This is clearly shown by values achieved for the WHO standard which is underestimated in the standard assay.

This is important, since the automated methodology including the standard BCS is performed in a large percentage of testing laboratories as stated above and the use of this type of methodology will be probably increasing in size. As is well known the automated methods are not the only methodology for assessing the vWF: Rcof activity.

As stated above there are a number of other methods that are in current use, that also show high variability in assessing potencies as well as plasma levels. At this point in time we believe that this clinical assay can accurately reflect the potency as well as the therapeutic factor levels in concentrates and plasma. This has been validated in the clinical lab at -(b)(4)- central Lab for the Wil-12 study.

We feel that our work in this field has improved the assay methodology for our product, and may help in moving the overall problem forward. In conclusion we believe that the Modified BCS is currently the most appropriate assay to be used for concentrate and plasma vWF: Rcof determinations. Concerning commercially available assays, we agree with the FDA, that an automated BCS assay is more suitable than a manual --(b)(4)-- assay as used in the first WIL-12 PK study determinations.

Enclosure 4: Wilate WIL-12 CSR supplement (PK sample re-analysis using an Automated Methodology) and Appendices; dated May 14, 2009.

Enclosure 17: Presentation of the Modified vWF: Rcof assay (BCS) ----(b)(4)- presentation slides included in the briefing package for the Wilate type A meeting with FDA scheduled for December 12, 2008.

Seimens AG BCS XP System and Modification of the Manufacturer's Assay for vWF: Rcof activity utilizing the BCS-XP System

Octapharma developed and submitted information for a new assay to determine vWF activity in Wilate samples. The new assay was the Behring (now Seimens) Coagulation System automated Coagulation Analyzer (BCS XP) SOP 130SOP154/00

"Determination of von Willebrand Factor in FVIII -----(b)(4)---samples by Ristocetin Cofactor Assay Using BCS XP".

In the presence of ristocetin the von Willebrand-Factor of the sample causes an agglutination of the stabilized platelets contained in the von Willebrand-reagent. The occurring agglutination reduces the turbidity of the sample. The change of the optical density at 570 nm is measured by the BCS XP instrument, and, based on the calibration curve, automatically converted into IU/mL.

Dade Behring was recently purchased by Seimens AG. The instrumentation has remained the same.

Octapharma has submitted a Modified BCS vWF: Rcof Activity Assay. This modified assay includes 2 changes to the manufacturer's recommended procedure. -----(b)(4)-----

Table: Recovery in Comparison to Ph. Eur. Manual Method

Analyzed Lot Of Wilate	Modified vWF:Rcof IU/mL (% of man.)	Manual vWF:Rcof IU/mL (%)	Original Automated vWF:Rcof IU/mL (% of man.)
Lot 1	92 (109)	84 (100)	72 (86)
Lot 2	61 (73)	84 (100)	43 (51)
Lot 3	80 (103)	78 (100)	65 (83)
Lot 4	83 (99)	84 (100)	58 (69)
Lot 5	89 (114)	78 (100)	52 (67)
Lot 6	84 (108)	78 (100)	56 (72)

Mod. vWF: Rcof = 1.10
Man. vWF: Rcof

Orig. Automated vWF: Rcof = 0.71
Man. vWF: Rcof

Validation of the Modified BCS Assay

Based upon the validation data supplied by Octapharma, the assay does appear to be adequately validated in regards to the assay's Precision, Linearity/Range, Accuracy and Limit of Detection. The Limit of Detection is the same as the well established automated methodologies. The Agency was informed by the company that the ---(b)(4)--- method was for the purpose of detecting lower limits for the PK studies and that the ----(b)(4)-- method would not be used in the normal process of assigning potency to production lots.

Data Summary on Testing of Wilate Batches Including FDA Test Results

Wilate	vWF:Rcof	vWF:Rcof	vWF:Rcof	vWF:Rcof		Comments (FDA)
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Lot #	Manual Method (Octapharma) IU/mL	Modified Assay (Octapharma) IU/mL	Original BCS Method (Octapharma) IU/mL	Testing Automated Method (FDA) IU/mL (%)	Test Date(s) (FDA)	
---(b)(4)---	84	119	64-93	86 (102.4%) 69 (82.2%) 78 (92.2%)	7/17/09, 7/24/09 7/29/09	Manual method potency used to determine dilutions
---(b)(4)---	84	99	53-81	85 (101.1%) 74 (87.8%) 79 (94.0%)	7/17/09, 7/24/09 7/29/09	Manual method potency used to determine dilutions
---(b)(4)---	84	97	51-79	88 (104.2%) 64 (76.3%) 72 (86.2%)	7/17/09, 7/24/09 7/29/09	Manual method potency used to determine dilutions
---(b)(4)---	84	108	51-82	77 (70.8%)	10/2/09	Modified method potency used to determine dilution
---(b)(4)---	92	92	52-82	78 (77.8%)	10/2/09	Modified Method potency used to determine dilution
---(b)(4)---	84	82	47-81	66 (80.0%)	10/2/09	Modified Method potency used to determine dilution

Review Comments/ Recommendation:

It is clear that test results included in chart “**Data Summary on Testing of Wilate Batches Including FDA Test Results**”, lot release test results utilizing the Modified BCS assay obtain relatively higher potencies than lots testing utilizing the manual or original (un-modified) BCS assays.

The manual and Original BCS potency values agree more favorably with test results obtained within the FDA testing facility. FDA test results for six lots tested, are more in line with potency results arrived at utilizing the Original BCS assay and the Manual methodology.

Octapharma's Modified vWF Activity assay utilizes an ---(b)(4)--- ristocetin final test concentration of -(b)(4)-. final conc. In the BCS vWF Reagent (which includes both platelets and ristocetin) supplied in the Siemens BCS assay test kit, the vWF Reagent has an approximate final ristocetin concentration of 0.8 mg. The reconstituted vWF Reagent (Siemens) has a shelf life of --(b)(4)--.

Octapharma also made a modification to the original BCS assay -----b)(4)-----

Recommendation

A recommendation that the BCS Modified Activity Assay for vWF as detailed by Octapharma not be approved as the assay methodology for the purpose of assigning potency values to the Wilate product.

The Manual vWF Activity Assay methodology appears to be an acceptable assay for the determination of vial potencies. This methodology was initially utilized for potency determination as well as for the PK study data. This methodology was not acceptable for the PK studies but is acceptable for potency value determination based upon lot release testing performed within the FDA test laboratory.

In a communication to the Agency dated November 2009, the Sponsor has agreed to the use of the Manual --(b)(4)-- methodology for the assignment of the vWF: Rcof Activity Assay potency. This assay methodology is acceptable.

Approval is recommended