



Mid-Cycle Meeting Summary
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Application: STN 125577
Product: von Willebrand Factor (Recombinant)
Proposed Indication: The proposed indication for rVWF is prevention and treatment of bleeding episodes in adults (age 18 years and older) diagnosed with von Willebrand disease.

Meeting Date and Time: May 22, 2015 at 10:00 am
Applicant: Baxter Healthcare Corporation
Committee Chair: Chava Kimchi-Sarfaty, PhD
RPM: Cherie Ward-Peralta

Attendees:

Chair Person: Dr. Chava Kimchi-Sarfaty – Not Present
CMC Product Reviewer: Dr. Zuben Sauna
Clinical Reviewer: Dr. Victor Baum
Clinical Pharmacology: Dr. Iftekhar Mahmood
Toxicology Reviewer: Dr. Anne Pilaro
Postmarketing Safety Epidemiological Reviewer: Dr. Meghna Alimchandani
Statistical Reviewer: Dr. Shuya (Joshua) Lu
APLB Reviewer: Dr. Loan Nguyen
DMPQ CMC & Facility Reviewer: Jie He
OCBQ/BIMO Reviewer: Colonious King
OCBQ DBSQC Representative: Hyesuk Kong
OCBQ DBSQC Representative: Marie Anderson and Josephine Resnick
OCBQ/DBSQC Reviewer: Dr. Lokesh Bhattacharyya
Regulatory Project Manager: Cherie Ward-Peralta

Additional Attendees:

Oiao Bobo, Team Lead, OCBQ/DMPQ/BII
Howard Chazin, MD, MBA, Deputy Director, DHCR, OBRR
John Eltermann, Director, DMPQ, OCBQ
Mahmood Farshid, PhD, Deputy Director, DHRR, OBRR
Basil Golding, MD, Director, DHRR, OBRR
Patricia Holobaugh, Chief, Bioresearch Monitoring Branch, OCBQ/DIS
Tim Lee, PhD, Acting Chief, Laboratory of Hemostasis (LH), DHRR, OBRR

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Ginette Y. Michaud, MD, Deputy Director, OBRR

Paul D. Mintz, MD, Director, DHCR, OBRR

Manette Niu, Acting Branch Chief, Pharmacovigilance Branch, Division of Epidemiology, OBE

Renee Rees, PhD, Lead Mathematical Statistician, Division of Biostatistics, OBE

Lisa Stockbridge, PhD, Chief, Advertising and Promotional Labeling Branch, OCBQ/DCM

Iliana Valencia, MS, RPM Staff Chief, OBRR

Peter Waldron, MD, Medical Officer, DHCR, OBRR

Mark J. Weinstein, PhD, Associate Deputy Director, OBRR

Please note the following agenda items for our mid cycle meeting for STN 125577/0. The goal of the Mid-cycle meeting is to have a comprehensive reading on the state of the review and pending actions for this original BLA subject to PDUFA V Program guidelines:

1. Reviewer Reports.

In general, the majority of the reviewers did not find any key finding or substantive issues. There will be a couple of requests for additional information to complete their reviews, but the reviewers do not foresee any major issues to arise with the responses to these questions. The reviewers that did have some key finding or substantive issues are listed below:

Pharmacovigilance Plan – Key findings and substantive issues:

Pharmacovigilance Plan (PVP)

Baxter proposes routine pharmacovigilance (PV) and labeling. Additionally, two phase 3 studies are planned (b) (4) which will collect additional safety data. Routine PV includes 15-day expedited reports for serious, unlabeled (unexpected) AEs and quarterly periodic safety reports for first three years following licensure (annual submissions thereafter).

Overview of the important identified and potential risks and proposed actions for PV are summarized in the table below.

Safety Concerns	Baxter Proposed Actions
Important Identified Risk: Hypersensitivity reactions	<ul style="list-style-type: none">▪ Routine PV and labeling▪ Planned Phase 3 clinical studies (b) (4)
Important Potential Risks: 1. Inhibitor formation 2. Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)	
Important Missing Information 1. Insufficient clinical data in children under 18 years of age 2. Insufficient clinical data on use in pregnancy and lactation 3. Insufficient clinical data on use in geriatric patients	Routine PV and labeling

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At this time, the proposed PVP is acceptable for the above identified and potential risks and missing information. Additional information on safety concerns is discussed below:

1. Hypersensitivity reactions: Important Identified Risk

A spectrum of hypersensitivity reactions from mild rash to life-threatening anaphylaxis may occur. Recombinant VWF is contraindicated in patients with known anaphylactic reactions to active substance, mouse or hamster proteins, or constituents of the product. Of note, VWD patients who develop inhibitor antibodies against VWF are at an increased risk to develop anaphylactic reactions after re-exposure to VWF.

Data: No severe hypersensitivity or anaphylactic reactions were reported in any subjects during the 3 completed clinical studies with rVWF. Possible hypersensitivity symptoms, including nausea (n=3), chest discomfort (n=1) and pruritus generalized (n=2) were reported in clinical studies.

PV Actions

- Passive surveillance of spontaneous AE reports, medical literature.
- Labeled in Package Insert under sections Contraindications, Warnings and Precautions, Clinical Trials Experience, Nonclinical Toxicology and Patient Counseling Information.
- Additional safety data will be collected regarding hypersensitivity reactions with rVWF in planned phase 3 clinical studies (b) (4)

2. Inhibitor formation: Important Potential Risk

Development of inhibitor antibodies is a potential risk of rVWF treatment. Depending on the level of inhibitor present, clinical manifestation may vary from non-serious asymptomatic lack of response to treatment to potentially serious life-threatening hemorrhage. Thus, patients using rVWF need to be evaluated by clinical parameters, with subsequent inhibitor assays, for the development of neutralizing antibodies. Additionally, in patients with high levels of inhibitors to VWF or FVIII, recombinant VWF may not be effective due to neutralizing antibodies, and this treatment may lead to severe adverse reactions. Of note, inhibitor antibodies may occur concomitantly with anaphylactic reactions, and patients who develop an anaphylactic reaction should be evaluated for inhibitors.

Data: None of the subjects treated in studies 070701 or 071001 developed neutralizing antibodies against rVWF or FVIII. However, in study 070701, 2/31 subjects had a high pre-infusion titer for binding anti-VWF antibodies of 1:1280 at screening that was confirmed for specificity. There were no treatment-related increase in antibody titers against VWF exposure and for both subjects the investigators did not report any changes in medical condition. All 37 evaluated subjects exposed to rVWF in study 071001 showed negative results for specific binding antibodies against rVWF. No subject had neutralizing antibodies against FVIII or rVWF after exposure in hemophilia A patients (study 071104). In addition, all 12 evaluated subjects exposed to rVWF in study 071104 showed negative results for specific binding antibodies against rVWF.

From this data, Baxter considers it to be a low risk for VWD patients to develop neutralizing or binding antibodies against rVWF. Also, potential impurities present in rVWF are considered to be low.

PV Actions:

- Passive surveillance of spontaneous AE reports, medical literature.
- Labeled in in Package Insert under sections Dosage and Administration, Warnings and Precautions, Patient Counseling Information.
- Assay will be available to measure presence of inhibitor antibodies to VWF or factor VIII in the clinical setting where expected plasma VWF activity levels are not attained, or if bleeding is not controlled with an appropriate dose.

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- Additional safety data will be collected regarding inhibitor formation with rVWF in planned phase 3 clinical studies (b) (4)

3. Thromboembolic events: Important Potential Risk

Thromboembolic reactions such as disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction, and stroke can occur, particularly in patients with known risk factors for thrombosis, including low ADAMTS13 levels, and concomitant overuse of FVIII.

Data: No thrombotic events occurred in any subject enrolled in clinical studies with rVWF.

PV Actions:

- Passive surveillance of spontaneous AE reports, medical literature.
- Labeled in in Package Insert under sections Warnings and Precautions.
- Additional safety data will be collected regarding thromboembolic events with rVWF in planned phase 3 clinical studies (b) (4)

4. Missing information on pediatric and geriatric patients, and lactating women are labeled in the Package Insert under section Use in Special Populations. Missing information on pregnant women (Pregnancy Category C: animal reproduction studies have not been conducted and no data on whether rVWF can cause fetal harm or affect reproductive capacity) is labeled in the Package Insert under sections Use in Special Populations and Nonclinical Toxicology.

Statistical Reviewers Key Findings:

Two clinical studies were submitted to this BLA submission, in which one study (071001) is considered the pivotal study according to the applicant.

Study 071001 was a phase 3, multicenter, part-randomized study. The primary outcome was the number of subjects with “treatment success” which was defined as a mean efficacy rating score of < 2.5 taking into account all bleeding episodes in a subject treated with rVWF during the study period. The success rate was prespecified as 65% and the result from 2-sided exact Clopper-Person 90% CI was (84.7, 100). So treatment with the investigational product is claimed efficient.

Analytical Methods for lot release testing of drug product and validation of the methods:

There are major deficiencies in the method validation for tests for critical quality attributes. To give a few examples of major deficiencies:

- a. Sponsor’s results for accuracy, repeatability, linearity, specificity, and robustness for the FVIII (b) (4) (b) (4) are not consistent with the current standard.
- b. The sponsor informed that they did not do accuracy evaluation of the vWF (b) (4) test because “spiking experiments could not be performed due to the nature of the method”. We do not agree that accuracy cannot be evaluated for an (b) (4) (b) (4). In addition, the data submitted for repeatability, intermediate precision, specificity and robustness are not consistent with the current standard.
- c. The sponsor provided accuracy data for moisture analysis (b) (4) using a (b) (4) but not the drug product.
- d. The linearity of the (b) (4) test was established using the standard. No linearity data was provided from the drug product.

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The deficiencies identified by DBSQC were discussed. The CMC (Product) reviewer and Deputy Director of DHRR clarified for DBSQC that the FVIII assay is included here to determine the residual level of rFVIII in the rVWF product, as a process-related impurity. Since the rFVIII level is expected to be very low and approaches the limit of detection, validating the assay in this range is extremely challenging. (b) (4)

DBSQC reviewer disagreed and indicated that FDA has provided guidance to the industry or validation of such assays through ICH Q2(R1) guidance document and method validation for similar assays are routinely included in support of BLA submissions. So, there is nothing unique about this assay. DBSQC reviewers felt that while they would continue to seek to resolve the issues of concern to them with Baxter, these are not likely to be show stoppers, particularly if the submission shows that the product is safe and efficacious. However, DBSQC will seek resolutions of the issues through PMC, as was done for a few other products. It was agreed that the chair of the BLA and CMC (Product) reviewer will discuss with DBSQC on details of the validation issues for the quality control lot-release tests for this product.

2. Will Discipline Review Letters be issued (for PDUFA V Program submissions)?

No Discipline Review Letters will be issued.

3. If the application will be discussed at an Advisory Committee, potential issues for presentation.

No, the Advisory Committee Meeting has been waived. Waiver Memo is complete and uploaded in the EDR.

4. Determine whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) are needed.

It was felt that the two proposed trials (b) (4) in addition to routine pharmacovigilance would suffice and that PMCs and PMRs are not indicated.

REMS will not be needed for this BLA.

5. National Drug Code (NDC) assignments to product/packaging.

- a. The 1st segment (NDC labeler code) is correct and appropriately assigned to Baxter Healthcare Corporation.
- b. The 2nd segment of the NDC code seems to be associated with a range of IU per vial. Cherie Ward-Peralta will discuss with Chave Kimchi-Sarfaty if this code needs to be unique to each IU per vial.
- c. The 3rd segments of the NDC are uniquely assigned to the package presentation for the vial and carton

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Color Code	VWF:RCO Potency Range	Vial NDC	Carton NDC	sWFI fill size
Green	450–850 IU per vial	0944-7551-01	0944-7551-02	5 mL
Dark Red	900–1700 IU per vial	0944-7553-01	0944-7553-02	10 mL
	Sterile Water for Injection	52919-005-05		10mL

6. Proper naming convention.

Dr. Kimchi-Sarfaty has accepted the current proper naming of this product as Von Willebrand Factor (Recombinant).

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval.

Facility inspections were performed at (b) (4)

The review team is awaiting responses to the FDA Form 483, but do not foresee any substantive issues that will prevent approval of the submission.

Confirm

8. Components Information Table was obtained and notification to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

Not Applicable for this submission.

9. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*. If not complete, indicate date it will be completed.

Mr. Jie He will review this information and finalize as stated in the Job Aid.

10. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

Lot release is not needed as this is a recombinant product. A completed testing plan is expected to be completed by late September 2015. Approval of the testing plan will depend on whether or not there are testing, labeling or naming issues on going that hold up finalizing the testing plan. DBSQC is hoping that samples will arrive by the end of June and testing will be completed in September 2015.

11. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01: Unique Ingredient Identifier (UNII) Code* for additional information.

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This action is pending by the RPM.

12. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.

PeRC is not needed since this is an Orphan Product.

13. Reach agreement on information to be included in the Mid-cycle communication with the applicant (see section below). The Mid-cycle communication is only for applications that qualify under the PDUFA V Program.

The communication document has been drafted and the tentative attendees from the review team are Dr. Kimchi-Sarfaty and Ms. Ward-Peralta.

Review

14. Major target and mile stone dates from RMS/BLA.

Mid-Cycle Review Meeting	May 29, 2015
MidCycle Communication with Applicant	Jun 11, 2015
Complete Discipline Reviews (Primary)	Jul 24, 2015
Complete Discipline Reviews (Secondary Review)	Aug 7, 2015
Send Late Cycle / Advisory Comm briefing package	Aug 21, 2015
External Late-Cycle Meeting	Sep 3, 2015
Promotional labeling review (APLB)	Sep 18, 2015
Complete inspection reports	Oct 19, 2015
Circulate draft press release	Nov 19, 2015
Complete PMC Study, Labeling Review, Review Addenda	Nov 19, 2015
Complete Supervisory Review	Nov 19, 2015
Request Compliance Check, Lot Release Clearance	Dec 4, 2015
Send Press Release to OCTMA	Dec 4, 2015
<i>T-minus date</i>	<i>Dec 4, 2015</i>
Send FDA Action Letter	Dec 18, 2015
Post-Action Debrief Meeting	Jan 11, 2016

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15. The status of the review for each discipline, inspection, EIR. If any primary reviews have not met the target date, provide the date the review will be completed. Include any consult disciplines.

Within the reviewer reports, most agreed to complete their primary review at the latest by July 24, 2015.

16. Discuss pending dates of targets and milestones (e.g. late-cycle meeting, Advisory Committee, labeling discussion).

No issues with pending target dates or milestones were presented by any of the review member of this meeting. Dr. Sauna requested if reviewers would agree to finalize their memos by the end of July to prepare for the Late-Cycle Meeting and to begin finalizing the labeling, final action letter, and SBRAs.

17. Establish a labeling review plan and agree on future labeling meeting activities.

After all review memos are completed, the review team can begin finalizing edits on the labels of the product.

Action items: No Action Items

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History: Cherie Ward-Peralta/ June 1, 2015
Zuben Sauna/ June 4, 2015
Victor Baum/ June 8, 2015
Lokesh Bhattacharyya/ June 8, 2015
Renee Rees/ June 16, 2015