



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

TO: To file BLA STN 125577/0

FROM: Jie He, M.S., CSO, CBER/OCBQ/DMPQ/MRBII

THROUGH: Marion Michaelis, Chief, CBER/OCBQ/DMPQ/MRBII

THROUGH: Jay Eltermann, M.S., Division Director, CBER/OCBQ/DMPQ

CC: Cherie Ward-Peralta, RPM, CBER/OBRR/PPMS

APPLICANT: Baxalta US Inc. [US. Lic#2020]

PRODUCT: Recombinant von Willebrand Factor; Vonicog alfa [VONVENDI]

SUBJECT: Addendum Review of the BLA submitted by Baxalta US Inc.
Lic. #2020, to provide for marketing of Recombinant von Willebrand Factor (rVWF)

ADD: December 19, 2015

REVIEW RECOMMENDATIONS

I recommend approval base on the review of the firm's response and additional information submitted.

REVIEW SUMMARY

Baxalta US Inc. (Baxalta) submitted an original application under STN 125577/0 for the licensure of recombinant von Willebrand Factor (rVWF) for the prevention and treatment of bleeding episodes in adults (age 18 years and older) diagnosed with von Willebrand disease. The BLA was received by CBER on December 19, 2014. The manufacture of rVWF is performed in the existing Baxalta establishments:

(b) (4)

Thousand Oaks (California, USA) site for final drug product.

Recombinant VWF is planned to be marketed as a unit kit containing one vial of rVWF, one vial of sterile water for injection (sWFI) as diluent, and one Mix2Vial reconstitution device which is 501(k) cleared. The Mix2Vial reconstitution device and the (b) (4) sWFI diluent have been previously approved and are currently in commercial use with other US licensed products for Baxalta.

This addendum memo covers DMPQ IR of July 30, August 15, August 19, August 27, and teleconference on September 11, 2015 and their correspondent amendments 12, 15, 18, 19 and 21.

As this is a recombinant product, this review was conducted under FDA's Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-derived Product or a Monoclonal Antibody Product for In Vivo Use. Under this guidance, limited

information is required to be submitted regarding facility and equipment. As such, my review is based on this guidance document.

REVIEW

FDA IR of July 30, 2015

FDA Question

(b) (4) acceptance limit for cleaning of (b) (4) is set at (b) (4) and actual data from all the process validation runs (b) (4) runs) reported (b) (4).

Please provide justification for the acceptance criteria and please also clarify if and what alarm limit has been established for this cleaning parameter.

Baxalta Response in Amendment 12, received on August 6, 2015

The (b) (4) acceptance criterion for cleaning of (b) (4) was set according to the compendial (b) (4) limit of (b) (4)

runs. A revalidation of the cleaning process was successfully performed in May 2015 (OR-20-0621-03-PQR.03), wherein a (b) (4) acceptance criterion of (b) (4) was met ((b) (4) samples of (b) (4) were used). Therefore, the (b) (4) acceptance limit for this cleaning parameter has been tightened to (b) (4), although (b) (4) will continue to be used as the (b) (4). This limit is consistent with (b) (4)

No alert limit is necessary since the (b) (4) acceptance limit is already consistent with the tighter compendial (b) (4) limit.

Reviewer's comment

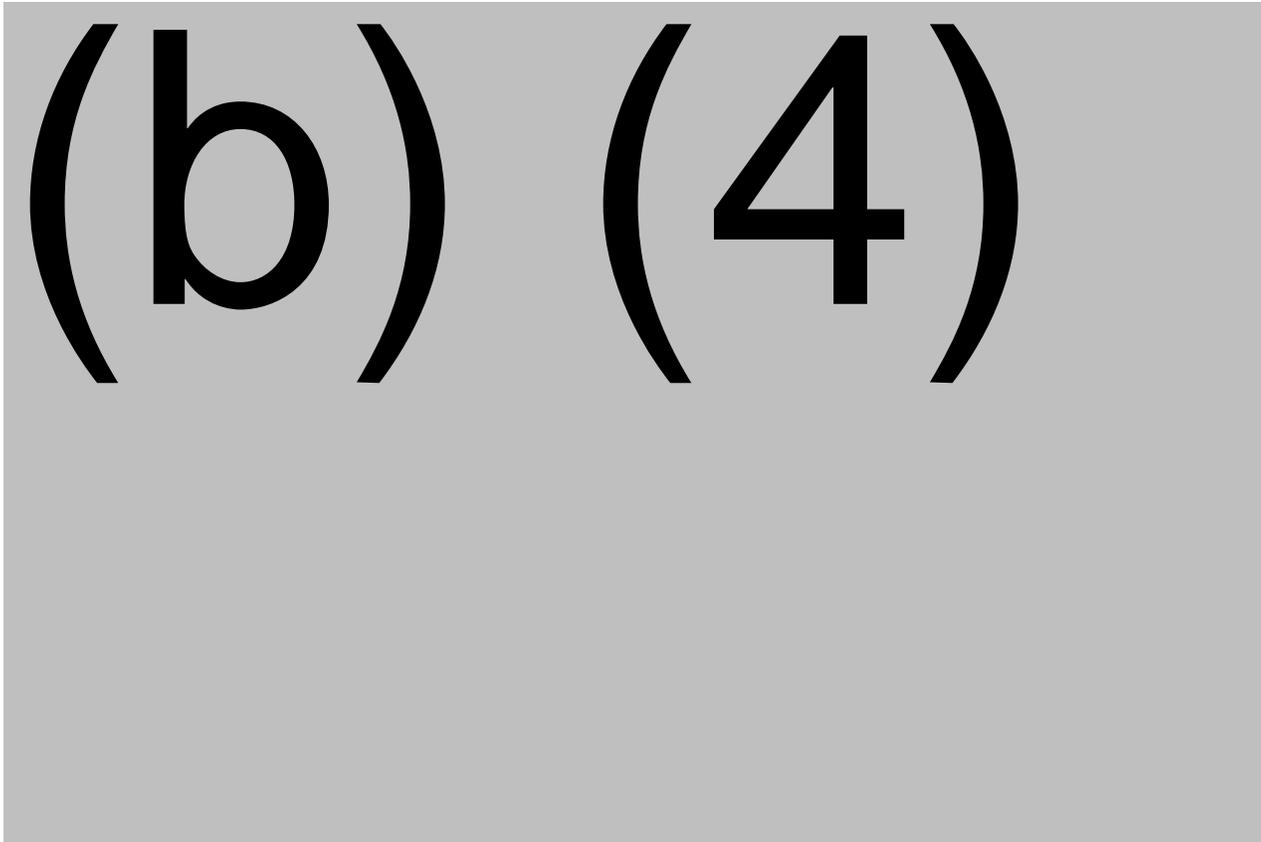
The (b) (4) limit has been revised to (b) (4) for the (b) (4), this is a significant improvement over the (b) (4) limit. The new limit is consistent with (b) (4) standard and reflects the actual process capability. The response is acceptable.

FDA IR of August 15, 2015

FDA Question

You stated that the acceptance criteria for (b) (4) of the (b) (4) WFI (b) (4) samples during cleaning validation were defined individually for each type of equipment at (b) (4). However, the reported acceptance criteria do not reflect the process capabilities as demonstrated by the results of the cleaning validation runs summarized in the table below. Please update your acceptance criteria to meet your process capabilities. Please justify your response.

(b) (4)



Baxalta Response received in Amendment 15 on August 27, 2015

Baxalta acknowledges FDA's request to update acceptance criteria to meet process capabilities. Cleaning process controls that reflect process capabilities have been established in (b) (4)

1. The Acceptance Criteria (AC) defines the maximum allowable amount of detectable residue after cleaning. The AL ensures safety of the product, is risk based, and is established in the validation plans. If the AL is exceeded, a formal investigation is initiated and the product impact is assessed.
2. The Control Level (CL) is defined to measure and monitor process capability. Following cleaning validation, process parameters are closely monitored. When at least (b) (4) data points are available, the CL is calculated statistically according to the formula:

$$\frac{(b) (4)}{\dots}$$

If the calculated CL is higher than the AL, then the AL is defined as CL. If the calculated CL is below the specification for (b) (4) then the CL is aligned with the (b) (4) specification.

If the CL is exceeded, a formal investigation is initiated.

Based on routine monitoring results obtained after cleaning validation, control limits that reflect observed manufacturing process capability have been established. These are provided in Table 1.

Table 1. Acceptance Criteria and Control Levels for (b) (4)

(b) (4)

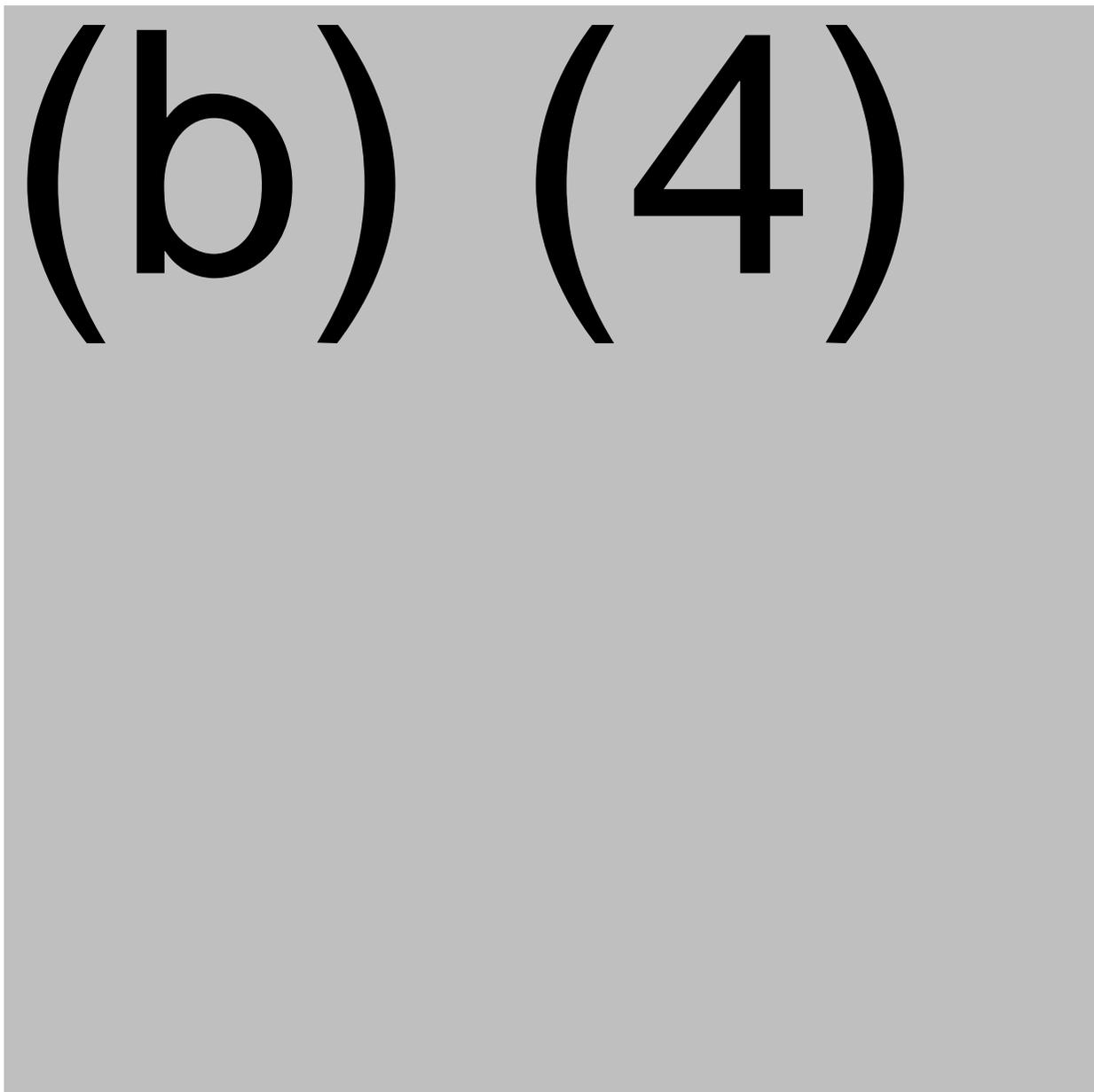
Reviewer's comment:

Baxalta provided a new "Control Level (CL)" for the cleaning process, which are based on actual cleaning results from at least (b) (4), in this amendment. The CLs are now closer in line with the process capabilities. The response did not address our concerns completely, since no sufficient rationales were provided for the high acceptable limits for (b) (4). A telecon was requested by FDA and was held on September 9, 2015 with Baxalta to discuss the response received in Amendment 15. FDA expressed concerns on how Baxalta can be sure that there is no carryover from any cleaning agents or from other materials, if the acceptance criteria are in a much higher range than the

(b) (4) standard. FDA expects the acceptance criteria to be much tighter than what Baxalta has presented. In particular, the acceptance criteria should be more closely aligned with the actual process capabilities. Baxalta was asked to provide rationales regarding the new “Control Level” implemented in the rVWF manufacturing process provided in the initial response, and explain the high acceptance limits for the (b) (4). Baxalta submitted Amendment 21 on September 16, 2015 to respond to the concerns for high (b) (4) limits for the (b) (4) samples.

Baxalta Response in Amendment 21 received on September 16, 2015 following the teleconference of September 9, 2015

Baxalta submitted updated acceptance limits for (b) (4) for the (b) (4) samples for equipment cleaning. The current acceptance criteria, as defined in a risk assessment, are based on process capability from routine data, as shown in the table below:



(b) (4)

Baxalta has confirmed that (b) (4) are dedicated to the rVWF production process.

Baxalta further explained their cleaning procedures for dedicated (b) (4) and (b) (4) sampling method, and the summarized in the table below:

(b) (4)

Baxalta stated that the (b) (4) are dedicated for (b) (4) use only, and the (b) (4) control limit corresponds to a concentration of (b) (4) in the (b) (4) WFI. Carryover of residue from one (b) (4) to another is negligible considering that the (b) (4) for the vWF intermediate products have significantly (b) (4) range for NaCl, CaCl₂, sodium citrate and (b) (4), for example). Therefore, there is no risk to the product and intermediates.

Baxalta will conduct periodical assessment of the cleaning limits based on process capability as part of the monitoring strategy to continue to evaluate and maintain the validation status. If the control level is found to be significantly below the acceptance criteria, the acceptance criteria are reduced based on a risk assessment and statistical and/or scientific data according to standard procedure.

Reviewer's comment:

The updated cleaning acceptance Control Limits are much closer aligned to their actual cleaning process capabilities. The rationales provided for the (b) (4) appear sufficient to justify the relatively high (b) (4) limits, and should pose minimal risk. The (b) (4) samples are monitored for all cleaning processes and Baxalta promised to continue assess the cleaning results and adjust the limits tighter when more data are available. The response is acceptable.

IR of August 27, 2015

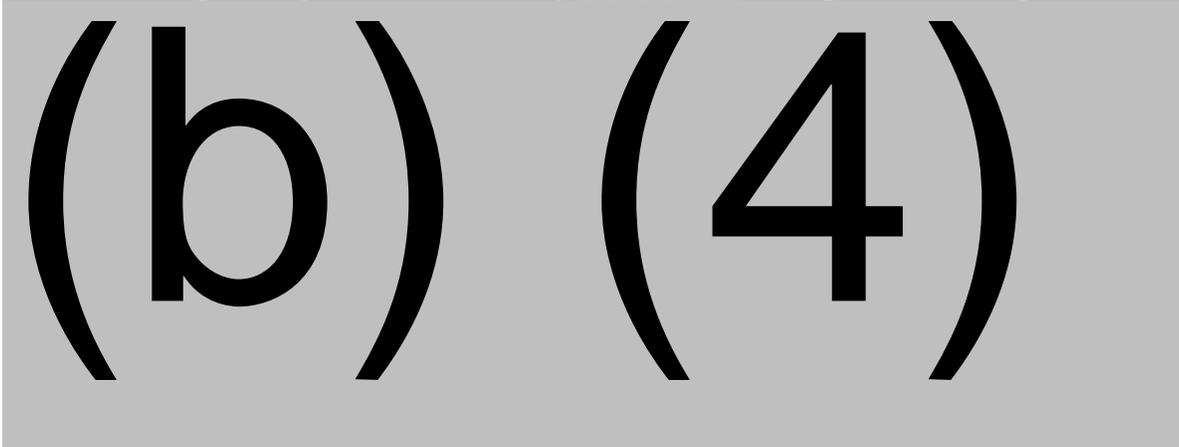
FDA QUESTION 1

Regarding cleaning validation at Thousand Oaks facility:

- a. You provided the acceptance criteria for your cleaning validation for equipment and small parts used for FDP manufacturing process (including items used for fill and finish processes, such as

(b) (4) as listed in the table below. You also provided data collected during the cleaning validation of some of the equipment except for the small parts. However, the current (b) (4) acceptance criterion does not reflect the process capabilities demonstrated by the available results from the cleaning validation runs. Please update your acceptance criteria for (b) (4) to meet your process capabilities. Please justify your response.

b. Please provide justifications on why (b) (4) is not part of the acceptance criteria.



Baxalta Response to Question 1, Amendment 19 received on September 11, 2015

a. (b) (4) samples for cleaning validation studies utilize a (b) (4) sample volume and results are reported by Quality Control Microbiology as (b) (4). As the Thousand Oaks facility is a multi-product manufacturing facility, the cleaning validation (b) (4) requirement is (b) (4) (b) (4) which is consistent with the most stringent manufacturing in-process (b) (4) limits established for the licensed products at the Thousand Oaks Facility. Historically, the facility has shown that (b) (4) levels do not increase during (b) (4) challenges and that the (b) (4) limit of (b) (4) ensures acceptable (b) (4) times for equipment (b) (4).

However, to ensure that cleaning processes performance are maintained within control, based on cleaning validation results, Baxalta is implementing a (b) (4) tolerance limit of (b) (4) for cleaning validation requalification criteria in the Formulation and Filling area. This tolerance limit is based on a statistical analysis including (b) (4) proportion of the population and at a (b) (4) confidence level using a total of (b) (4) samples collected from (b) (4). This tolerance limit ensures the cleaning process is effective, capable and remains in control. Exceeding the tolerance limit provides indication of a departure from expected performance and requires an evaluation for the potential root cause. However, exceeding the tolerance limit of (b) (4) does not necessarily suggest an impact to product quality as the acceptance criteria of (b) (4) is based on in-process manufacturing limits and is further reduced by subsequent (b) (4) processes that are validated to show a (b) (4) of the test organism.

Reviewer's comments:

Baxalta has (b) (4) the (b) (4) limit from (b) (4) based on their accumulated data from manufacturing operations. Since there is another (b) (4) process for

at least of a (b) (4) before equipment will be used, (b) (4) is well monitored and controlled. The response is acceptable.

- b. Prior to production use, small parts (b) (4) and other auxiliary non-product contact small parts) are cleaned with (b) (4). During the original validation of the small parts (b) (4) procedure, summarized in Section 2.1 of 3.2.A.1 Facilities and Equipment [*Equipment Cleaning – Formulation and Filling Complex* (b) (4) analysis was used to evaluate the effectiveness of (b) (4) procedures by detecting trace quantities of basic or acidic compounds present in the cleaning process. Since (b) (4) was determined to be the most appropriate method to determine residues of this cleaning agent, instead of (b) (4) found in P98-123-01-VQ, Validation of (b) (4) of Cleaning Agents, indicate that WFI has an average (b) (4) has an average (b) (4). Subsequent to the original validation of the small parts (b) (4) procedure, Baxalta committed to testing all equipment cleaning (b) (4) samples to (b) (4) standards (with the exception of (b) (4)) as part of the Comparability Protocol for the planned introduction of clinical products in Formulation and Filling Complex (b) (4) [primary STN: BL 103375/5315 approved 15 March 2010). Therefore, (b) (4) was included as a cleaning acceptance criterion during the supplementary validation performed for rVWF per Protocol TO-67-0776N001, Performance Qualification of the Fill Line (b) (4) Small Parts (b) (4) Cleaning – rVWF Manufacturing Confirmation, as shown in Table 2.



Reviewer's comments:

The justification provided for using (b) (4) as a measurement for the cleaning acceptance criterion for the equipment cleaning is acceptable. The supplemental validation study results also provided assurance the cleaning process is validated.

FDA QUESTION 2

Regarding (b) (4):

- a. Please clarify if (b) (4) are dedicated to rVWF or shared with other products.
- b. Please provide the cleaning validation data for (b) (4)

Baxalta Response to Question 2

- a. The (b) (4) are shared amongst clinical and commercial products in which the active ingredient is manufactured utilizing (b) (4) that do not include animal proteins and the final container (b) (4) does not contain (b) (4)

derived from human plasma; i.e. recombinant Factor VIIa (rFVIIa), recombinant Factor IX (rFIX), and recombinant von Willebrand Factor (rvWF).

(b) (4)

(b) (4)

The original and supplementary cleaning validation demonstrated efficacy of the cleaning procedure to effectively clean small parts, reducing specific residues to an acceptable level as defined per Protocols TO-67-0652R and TO-67-0776N001.

(b) (4)

(b) (4)

The response is acceptable.

FDA IR of August 17, 2015

FDA Question 1

Please provide shipping validation and stability studies for rFurin.

**Baxalta Response to Question 1, Amendment 18 received on September 2, 2015
Container Closure System [rFurin]**

(b) (4)

