

MEMORANDUM



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



To: Administrative File (STN 125512/0)
Thomas Maruna, MS, MLS(ASCP), OBRR/IOD/RPMS

From: Natalya Ananyeva, PhD, Laboratory of Hemostasis (LH)
Division of Hematology Research and Review (DHRR)/OBRR

Through: Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR

Basil Golding, MD, Division Director, DHRR/OBRR/CBER

Subject: Final Review of the CMC Information in the Original Biologics License
Application from Baxter Healthcare Corporation for Antihemophilic Factor
(Recombinant), Porcine Sequence [OBIZUR]

INTRODUCTION

Baxter Healthcare Corporation (Baxter) submitted an original Biologics License Application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant), Porcine Sequence. The proprietary name of the U.S. marketed product is OBIZUR.

OBIZUR is indicated for the treatment of bleeding episodes in patients with acquired hemophilia A (AHA). OBIZUR is not indicated for the treatment of congenital hemophilia A or von Willebrand disease.

The active component in OBIZUR is a recombinant (r) analogue of porcine (p) Coagulation Factor VIII (FVIII) in which the B-domain of the molecule was replaced with a twenty-four amino acid linker. There is a high degree of sequence homology between porcine and human FVIII which have identical domain structure A1-A2-B-A3-C1-C2. Similar to its human counterpart, pFVIII is synthesized as a single chain and prior to its secretion is processed intracellularly to the heavy chain (A1-A2-B) and the light chain (A3-C1-C2), which are non-covalently linked via metal ion bridge. The linker in rpFVIII represents the N-terminal twelve and the C-terminal twelve amino acid residues of the B-domain of pFVIII.

The safety and efficacy of OBIZUR were evaluated in a prospective, open-label, multicenter clinical trial of 29 subjects with AHA who received OBIZUR to treat a serious bleeding episode. All subjects evaluated for efficacy (n = 28) had a positive response to treatment at 24 hours after dosing for the initial bleeding episode. No safety concerns were identified in the trial.

BACKGROUND

Acquired hemophilia A (AHA) is a rare bleeding disorder which does not have a genetic or heritable cause but occurs when the body develops inhibitory antibodies to its own human FVIII, thus creating FVIII deficiency and preventing normal hemostasis. The bleeding episodes in patients with AHA may be spontaneous and severe at presentation, and they may be life-threatening. The clinical manifestations of AHA include spontaneous hemorrhages into skin, muscles, soft tissues, or mucous membranes. AHA affects both males and females and is associated with significant morbidity and mortality.

Recombinant activated factor VII (rFVIIa, NovoSeven) is licensed in the U.S. for treatment and peri-operative management of bleeding in adults with AHA. However, the short half-life of rFVIIa (approximately 2.5 h) and the risk of thrombotic events, as well as the absence of adequate biomarkers that can correlate with clinical outcome, are limitations in the clinical use of “bypassing” agents. In addition, monitoring efficacy by means of standard measures of coagulation, such as prothrombin time or activated partial thromboplastin time, is not useful in this case.

The principle of using pFVIII is based on its low cross-reactivity with anti-human FVIII antibodies due to sequence variations between human and pFVIII in the A2 and C2 domains, the main targets of FVIII inhibitors. The cross-reactivity of inhibitory antibodies to human FVIII with pFVIII is estimated at 15% in patients with congenital hemophilia A, and is even lower in patients with AHA. When administered to patients with AHA, pFVIII is less likely to be bound by inhibitory antibodies and can function in the coagulation cascade to promote hemostasis.

Plasma-derived pFVIII (marketed as Hyate:C under U.S. License 1609) has been licensed in the U.S. since 1980 to achieve hemostasis in patients with anti-human FVIII inhibitors. However, the commercial production of Hyate:C was discontinued in 2005 due to problems with sourcing suitable porcine plasma and reported product immunogenicity. Therefore, OBIZUR may address the clinical need for a FVIII-based product for use in patients with AHA.

Regulatory History

OBIZUR was developed under Investigational New Drug (IND) application, IND 10695,

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-----The early development and Phase I clinical lots of Drug Substance (DS) were manufactured by a contract manufacturing organization ----- (b)(4) -----

----- and Drug Product (DP) was manufactured by ----- (b)(4) -----.

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

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In January 2010, Ipsen sub-licensed the OBI-1* program to Inspiration Biopharmaceuticals, Inc. (Laguna Niguel, CA, USA), and Inspiration assumed the ----- (b)(4) -----.

quality at the end of shelf-life. The current specifications for DS and DP are adequate to control the identity, purity, potency, and safety of OBIZUR.

6. The results of Batch Analyses encompass over (b)(4) DS and 25 DP commercial-scale batches and support consistent performance of the manufacturing process to produce OBIZUR that meets pre-determined quality specifications. As a well-characterized recombinant product, OBIZUR is exempted from routine lot-by-lot release by CBER. Baxter has demonstrated its ability to adequately control the manufacturing process, and consistently produce product lots of established quality. In-support testing by CBER confirmed the results of batch analyses for PV DP lots reported in the BLA and the suitability of critical quality-defining methods for their intended use as lot release tests.
7. The life-cycle of the manufacturing process is managed through a Process Monitoring Program and Process Control strategy which include --(b)(4)-- product review/product quality review, management of deviations, non-conformances, corrective action and preventive action (CAPA) system, and other quality system components.

RECOMMENDATION

The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls in the BLA and has adequately addressed the requests from all CMC reviewers in Amendments 17, 21, 24, 29, 37, and 42. The manufacturing process for OBIZUR, Antihemophilic Factor (Recombinant), Porcine Sequence, is considered to be adequately validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the commercial product that meets the release specifications. The manufacturing process provides acceptable safety margins regarding adventitious agents. All the issues, identified during the inspections of the facilities in -----(b)(4)----- have been satisfactorily addressed.

I and other CMC reviewers from the Division of Hematology Research and Review, OBRR, recommend **APPROVAL** of the BLA for Antihemophilic Factor (Recombinant), Porcine Sequence [OBIZUR].

The Clinical reviewer concluded that the submitted clinical data demonstrate the safety and efficacy of OBIZUR for the proposed indication. Bioresearch Monitoring inspections support the validity and integrity of the clinical data.

MANUFACTURING FACILITIES

Facility	Manufacturing Operations
Baxter Healthcare Corporation Baxter ----- ----- ----- -----(b)(4)----- -----	Manufacture of -----(b)(4)----- --- (cell culture – -----(b)(4)----- ----- --- (b)(4) -- qualified facilities for storage of MCB and WCB All IPC and QC release testing of (b)(4) (excluding Adventitious Agent and Mycoplasma testing)
----- ----- ----- -----(b)(4)----- -----	Manufacture of DP (sterile filtration, filling, lyophilization, over-sealing and inspection). All IPC and QC release testing (excluding ---- (b)(4)----- testing and excipients testing other than Polysorbate 80)
----- -----(b)(4)----- ----- ----- -----	Vial labeling and secondary packaging of DP
----- ----- -----(b)(4)----- ----- ----- -----	Manufacture of 1 mL pre-filled diluent syringe with Sterile Water For Injection
-----, -----(b)(4)----- -----	Manufacture of 1 mL pre-filled diluent syringe with Sterile Water For Injection

Additional Contract Testing Sites	Testing Tasks
-----, -----(b)(4)----- ----- -----	-----(b)(4)-----
-----, -----(b)(4)----- ----- ----- -----	-----(b)(4)-----
-----(b)(4)-----	-----(b)(4)-----

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Applicant in the 4 April 2014 Information Request. Baxter performed the review and new trend analyses of all accumulated manufacturing data and tightened or more clearly defined CPPs and IPCs in Amendments 17 (25 April 2014) and 24 (27 June 2014):

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The revised in-process controls (CPPs and IPC tests) (Module 3.2.S.2.4 in Amendment 17) are acceptable and can ensure stringent controls over the manufacturing process and its robustness within the proven acceptable ranges in delivering DS batches of consistent yield, purity and potency.

HOLD TIMES

The process step hold times in the manufacture of DS are described in Modules 3.2.S.2.4, Control of Critical Steps and Intermediates and 3.2.S.2.6, Manufacturing Process Development and in Amendment 11 (27 February 2014). Hold times were also discussed during the -----
-----~~(b)(4)~~----- The original study reports were provided for my review and are referenced below.

The DS manufacturing process does not have distinct process intermediates per the ICH Q5C definition. However, there are -----~~(b)(4)~~-----
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Reviewer’s Comments

Baxter’s validation strategy for the DS manufacturing processes is consistent with the recommendations in ICH Guidelines Q7 and Q11. The validation studies for the DS manufacturing process were performed at Baxter’s (b)(4) facility, the intended commercial site, under a prospective process validation protocol, which encompasses all stages of the DS manufacturing process, ----- (b)(4) -----

----- The process was validated by production, at commercial scale, of three consecutive DS PV batches. All pre-defined acceptance criteria stated in the Protocol (for CPPs, hold times, IPC and release testing) were met. The deviations were addressed adequately and do not affect the validity of the results. All three PV lots were dispositioned as “Released” by QA following the established procedures. Thus, the results of the validation studies fulfill the requirements for a successful process validation.

A more general perception of process performance consistence was gained from my review of the following:

- The results of Batch Analyses presented in Module 3.2.S.4.4 in the BLA that included one nonclinical, five Phase I/II clinical, over 30 Phase III clinical (pre- and post-validation from OBI-008 to OBI-047) and three PV batches;
- Original *Certificates of Analyses* (CoA) during the (b)(4)- PLI for the (b)(4) Batches ----- (b)(4) ----- which included Phase III Clinical, Validation and Post-Validation batches;

- Executed Batch Record for PV Batch ---(b)(4)--- which reflected adequate documentation of process steps (CPPs and Hold Times), adequate introduction of equipment, media and buffers into the process, and adequate sampling for relevant IPC tests (Bill of Testing).

All release results were within the pre-defined specification ranges and were consistent between the original CoAs and the information in the BLA; notably, the ranges in the commercial (b)(4) Specification for all parameters are qualified in Phase III clinical studies. Based on the evaluation of the manufacturing and testing data for the Phase III clinical, PV and post-validation batches of DS, the manufacturing process for OBIZUR DS is found to be well controlled, adequately validated and consistent in producing DS batches of the required quality at full manufacturing scale at Baxter’s (b)(4) facility.

CHARACTERIZATION: ELUCIDATION OF STRUCTURE AND OTHER CHARACTERISTICS

Structural characterization and elucidation of the physico-chemical properties of rpFVIII are described in Module 3.2.S.3 Characterization in the BLA. The characterization studies were performed on selected clinical batches of DS and DP representing different stages of process development, and rpFVIII reference material.

The active ingredient in OBIZUR is a recombinant analogue of pFVIII, ----(b)(4)-----, with an approximate molecular weight of 170 kDa. In rpFVIII, the B-domain was replaced with a twenty-four amino acid linker representing twelve N-terminal and twelve C-terminal amino acid residues of the pFVIII B-domain. The rpFVIII molecule is expressed as a single-chain glycoprotein which is intracellularly processed and is secreted as a metal ion-linked heterodimer with a 90-kDa heavy chain (HCh) and an 80-kDa light chain (LCh).

Figure 1. Structure of Recombinant Porcine Factor VIII (B-Domain Deleted)

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Potency by One-Stage Clotting Assay

The OC assay for determining the potency of rpFVIII is based on its ability to shorten the prolonged coagulation time of FVIII deficient plasma. The assay is derived from, and similar to, the activated partial thromboplastin time (aPTT) assay. The rate of clot formation is measured as a function of turbidity through monitoring light scattering at 660 nm. The time required to achieve the light intensity plateau is defined as the coagulation time which is proportional to the level of FVIII in the sample.

For characterization, ----(b)(4)----- and (b)(4) and DP Lots --(b)(4)-- and ---(b)(4)-- were tested in the OC assay. All samples demonstrated the ability of rpFVIII to be activated by human thrombin and react with human FIXa to initiate the coagulation cascade, leading to clotting of FVIII-deficient human plasma. The clotting activity was consistent for the -----
----- (b)(4) ----- DP lots (around the target potency of 500 U/mL).

Baxter validated the OC assay for potency assignment of rpFVIII DP based on the analytical and clinical data that demonstrate the assay’s suitability and consistent performance, and the general availability of this assay in clinical laboratories. For the OC assay, Baxter uses human FVIII deficient plasma from -----(b)(4)-----, and rpFVIII in-house Reference Standard for potency --- (b)(4) ---- calibrated against the WHO 8th International Standard for FVIII concentrate which is of human origin.

Potency by Chromogenic Substrate Assay

The CS assay is based on the activation of FX by FIXa in the presence of thrombin-activated FVIII, phospholipid surface and calcium ions. The amount of FXa is assessed from its ability to hydrolyze the chromogenic substrate, thus liberating the chromophore para-nitroaniline (pNA). The amount of released pNA correlates with the FVIII content.

(b)(4) uses FVIII Chromogenic Assay kit from -----(b)(4)-----
----- and (b)(4) in-house reference standard for potency --- (b)(4) ---- calibrated against the WHO 8th International Standard for FVIII concentrate.

Reviewer’s comments

Baxter’s characterization program was comprehensive and utilized an extensive panel of state-of-the-art analytical methods to evaluate the structure and function of the rpFVIII product. The primary structure of rpFVIII was confirmed by -----
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Other process-related impurities include -----
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----- (b)(4) ----- The process mapping and spiking studies along with the historical batch analysis data demonstrated that the (b)(4) manufacturing process consistently removes these impurities to levels well below the LOD of the respective assays. Calculations based on the worst-case scenario show that these levels are significantly lower than the maximum permitted daily exposures according to WHO and ICH guidelines. These impurities are not tested at the release of the DS and the provided evidence cited above justifies this decision.

Product-related impurities – ----- (b)(4) -----
----- – are controlled through release testing of the --- (b)(4) -- DP (further discussed under DP Specification).

SPECIFICATION FOR DRUG SUBSTANCE (MODULE 3.2.S.4.1)

Baxter’s approach and principles for establishing the release specifications for DS are described in Module 3.2.S.4.5 in the BLA and were also discussed during the (b)(4) PLI with -----
----- (b)(4) -----.

On my request, Report 112178-RPT/2.0 “*Justification of Specifications for OBI-1*” was provided for my review and was subsequently submitted to the BLA in Amendment 21 (22 May 2014).

The parameters were selected from the critical quality attributes determined in the process development studies and risk assessments. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data.

The manufacturing capability was assessed through statistical analysis of the release and stability (where applicable) data for the Phase III Clinical and Process Validation batches (from --- (b)(4) ----- representative of the commercial process. The upper and lower specification limits (USL and LSL, respectively) were calculated on the basis of the mean of the dataset, plus and minus the appropriate Tolerance Intervals. The Tolerance Intervals were calculated with --- (b)(4) --- using ‘95 % confidence level’ and ‘minimum 99 % of population in interval’ options as this gives an acceptable level of confidence.

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DESCRIPTION AND COMPOSITION OF DRUG PRODUCT

OBIZUR is supplied as a white lyophilized powder in single-use vials that nominally contain 500 units per vial in 1-vial, 5-vial, and 10-vial package sizes. Each package contains an appropriate number of each of the following components correlating to the vial package size: single-use vial of OBIZUR, pre-filled syringe with 1 mL SWFI, and vial adapter with filter.

Each vial of OBIZUR is labeled with the actual rpFVIII activity expressed in units determined by a one-stage clotting assay, using an rpFVIII reference material calibrated against the World Health Organization (WHO) 8th International Standard for FVIII concentrate, which is of human origin as discussed under DP Specification. Qualifying the product-specific standard against the WHO International Standard provides a linkage to the publicly available reference standard that is relevant to the potency of this product. This also allows for traceability for future product-specific standards.

OBIZUR is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with SWFI. The reconstituted product contains rpFVIII and the following components per mL: 8.8 mg sodium chloride, 0.04 mg Tris-base, 0.73 mg Tris-HCl, 1.47 mg tri-sodium citrate dehydrate, 0.15 mg calcium chloride dehydrate, 1.9 mg sucrose, and 0.05 mg polysorbate 80.

Container and Closure

The container closure system for OBIZUR consists of the following components:

- 3 mL clear ----(b)(4)----- glass vial conforming to -----(b)(4)-----
----- glass specification
- 13 mm butyl rubber stopper -----
----- (b)(4)----- rubber closures
- Sterile 13 mm aluminum over-seal with polypropylene flip top

For further details on the container closure system for DP and its integrity testing, please refer to the memorandum of the DMPQ reviewer.

MANUFACTURING PROCESS AND PROCESS CONTROLS FOR DRUG PRODUCT

OBIZUR DP is manufactured at the -----(b)(4)-----
----- . The DP manufacturing process consists of the ----(b)(4)-----,
sterile filtration, filling, lyophilization, and over-sealing. Labeling and secondary packaging is
performed at Baxter’s facility in -----(b)(4)-----.

The process flow for DP is described in Module 3.2.P.3.3 in the BLA and was observed by the
FDA inspectors during the ----(b)(4)----- facility PLI. IPCs are described in the BLA in
Module 3.2.P.2.3, Manufacturing Process Development and Module 3.2.P.3.4, Control of
Critical Steps and Intermediates. In-process controls and processing (hold) times were also
discussed during the PLI with -----(b)(4)-----
----- . Justifications for the established allowable processing times are
summarized in the technical report PRV-RP-TR(1)-002/027 “*Review of Data to Support the
Time Limitations associated with the OBI-1 Manufacturing Process*”.

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Sterile Filtration (defined as Date of Manufacture)

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The validation of the sterile filtration process for DP was performed by (b)(4)- in accordance
with FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing -
Current Good Manufacturing Practice (2004). The validation studies are summarized in (b)(4)
Report PRV-RP-VSR (2)-002/113 “*Validation Summary Report for the Sterile Filtration of OBI-
1 Drug Products*”.

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Of note, the initial validation of the lyophilization process was found inadequate in that no product temperature mapping was performed. A new protocol was generated and executed by the Applicant; the results were submitted to the FDA in the revised Commercial Lyophilization Performance Qualification Report (Amendment 33 dated 19 September 2014); the results were reviewed and found to be acceptable. Please refer to the memoranda of the DMPQ reviewer (Dr. Qiao Bobo) for further details.

Over-Sealing

The vials with lyophilized DP are loaded onto the filling machine for over-sealing with pre-sterilized aluminum seals which are preliminary loaded into the hopper. Vials are examined for over-seal integrity, samples are taken for release testing of DP, and the trays with vials are transferred to an (b)(4) area for collation into boxes, and are stored 5°C until shipment to Baxter's ---(b)(4)-----.

There is no reprocessing or reworking of the OBIZUR DP.

Labeling

Labeling and secondary packaging is performed at Baxter's facility in ---(b)(4)-----. Of note, in the initial submission, the validation of shipping procedures for DS and DP between the manufacturing sites was incomplete or the procedures were not established. In the course of the review, the Applicant completed the qualification of the transport process; the reports submitted in Amendments 27, 29 and 30 were reviewed by the FDA and found satisfactory. Please refer to the memoranda of the DMPQ reviewer (Dr. Qiao Bobo) for further details.

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[(b)(4)]

Reviewer’s Comments

In the original submission, a number of reports to support the processing times were missing. On my request, the Applicant submitted the reports, discussed above, in Amendment 21 (22 May 2014). The CPPs, IPCs and process time limits for the DP manufacturing process were initially determined based on the results of process development multivariate studies and process simulation studies that established time limitations for maintaining sterility assurance. The control parameters were verified through the in-process, release and stability testing of Phase III Clinical and PV DP batches. Based on the review of the information in the BLA and Amendment 21, the selected CPPs and IPC tests assure adequate control over of the manufacturing process and its robustness within the proven acceptable ranges in delivering DP batches of consistent yield, purity and potency.

MANUFACTURING PROCESS DEVELOPMENT AND CHANGES

The manufacturing process development is described in Module 3.2.P.2.3 in the BLA and was also discussed during the ---(b)(4)----- PLI with ----(b)(4)-----, specifically, manufacturing changes implemented after transfer of the DP process to the ----(b)(4)----- . The OBIZUR DP used in Phase I and in early Phase II clinical studies was manufactured by ----(b)(4)-----, using (b)(4) manufactured by ----(b)(4)----- . During Phase II, the DS manufacturing process was transferred to ----(b)(4)-----, and the DP process was transferred to the ----(b)(4)----- was upgraded with new equipment in 2007; Phase III clinical supplies have been manufactured since 2009 at this site, which is also intended for commercial supply of OBIZUR DP.

The DP manufacturing process remained essentially the same after transfer to the ---(b)(4)----- facility; with the following changes intended for process optimization:

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In both series of the validation studies, all operational control parameters and critical process parameters were within operating limits and the results of in-process control tests met acceptance criteria. The results of the release testing were within Specification for all (b)(4) batches. In the 2012 series, there were two discrepancies and three unplanned events associated with the first PV batch (b)(4)-- which were adequately addressed. To ensure the reliability of the results of the 2012 campaign, the (b)(4) PV batch (b)(4) was manufactured. During the manufacture of the 2013 batch (b)(4), there was one discrepancy and one unplanned event which were adequately addressed. All (b)(4) lots were dispositioned as “Released”.

Reviewer’s Comments

The following issues were resolved in the course of the review. The original submission provided only the summary of the 2012 studies but did not include the original process validation study reports for the 2012 and 2013 process validation campaigns to support the conclusions in the BLA. These reports were provided for my review during the PLI. On my request, the following original study reports were submitted to the BLA:

- Report PRV-RP500-PVR(2)-002/116 “*Process Validation Report for the OBI-I Drug Product 500 Units/vial Manufacturing Process in the --(b)(4)---- Facility*” (2012 series of the validation studies, Amendment 21)
- Report PRV –RP500-PVR2(1)-002/116 “*Process Validation Report for the OBI-I Drug Product 500 Units/vial Manufacturing Process in the --(b)(4)---- Facility*” (2013 series of the validation studies, Amendment 42 dated 10 October 2014)
- PRV-RP500-VSR(2)-002/116 “*Process Validation Summary Report for the OBI-I Drug Product (500 Units/vial) Secondary Manufacturing Process in (b)(4)-*” (2014 comparative analysis of the results from both series against commercial in-process and release specifications, Amendment 42)

Based on my review of these reports, Baxter’s validation strategy for the DP manufacturing processes is consistent with the recommendations in ICH Guideline Q8. The validation studies

were performed at ---(b)(4)---- facility, the intended commercial contract facility, under a prospective process validation protocol. In both the 2012 and 2013 series of validation studies, process (CPPs) and quality (IPC tests) controls for DP PV lots complied with the prospectively defined acceptance criteria and the results of release testing were within the specifications established for the commercial product. This fulfills the requirements for a successful process validation.

To gain a more general perception of process consistency, I reviewed the results of batch analyses reported in the BLA (Module 3.2.P.5.4) and original test results in the CoAs for the Phase III Clinical, PV and subsequent post-validation batches of OBIZUR during the PLI. All CoAs complied with the Specifications that were in place at the time of lot manufacture and matched the data in the BLA. However, the data in the CoAs did not match the data that were used to establish the acceptance criteria for commercial DP specifications (Section 3.2.P.5.6 Justification of Specification in the BLA and Report 112178-RPT discussed under DP Specification). (b)(4)/Baxter explained that the difference was due to the re-evaluation of the data for the parameters determined by the -----(b)(4)----- methods (due to the change in -----(b)(4)---- criteria discussed under DS Specification) and adjustment of FVIII Activity values (by the CS assay) for the current Potency Reference Standard ---(b)(4)----- (discussed under DP Specification).

During the PLI, I reviewed the documents related to the implementation of these changes and concluded that the chain of actions occurred in an adequate timely manner. On my request, (b)(4)/Baxter submitted the original Report 112178-RPT (version 2.0) “*Justification of Specifications for OBI-I*” with both the original and re-calculated data to the BLA file in Amendment 21. The results of batch analyses for the Phase III Clinical, PV and post-validation lots met the Specification for the commercial product.

In summary, based on the evaluation of the manufacturing and testing data for the Phase III clinical, process validation and post-validation batches of DS and DP, the manufacturing process for OBIZUR is found to be well controlled, adequately validated and consistent as evidenced by:

- Identification of CPPs and validation of their operating ranges;
- Identification of IPC and release tests and validation of their acceptance criteria;
- Robustness of the manufacturing process steps within the proven acceptable ranges;
- Extensive characterization of DS and DP batches, representative of different stages of process development, and their comparability;
- Satisfactory release data for over (b)(4) DS and over 25 DP batches (commercial scale), including IPC and release test results of all PV batches, that meet the pre-determined criteria for quality characteristics;
- Availability and adherence to SOPs as verified during the two pre-license inspections.

SPECIFICATIONS FOR DRUG PRODUCT (MODULE 3.2.P.5.1)

The approach and principles for establishing the release specifications for DP are described in Module 3.2.P.5.6 in the BLA, and were also discussed during the ---(b)(4)----- PLI with -----
----- (b)(4)-----

			----(b)(4)-----
	Endotoxin	----- (b)(4)-----	----(b)(4)-----
Excipients	Sodium	----(b)(4)-----	----(b)(4)-----
	Calcium	----(b)(4)-----	----(b)(4)-----
	Citrate	----(b)(4)-----	----(b)(4)-----
	Chloride	----(b)(4)-----	----(b)(4)-----
	Tris	(b)(4)	----(b)(4)-----
	Sucrose	----(b)(4)-----	----(b)(4)-----
	Polysorbate 80	----- (b)(4)-----	----(b)(4)-----

Reviewer’s Comments

The specifications for DS and DP are established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from critical quality attributes determined in the process development studies and risk assessments. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data. The manufacturing capability was assessed through analysis of release and stability (where applicable) data for the Phase III clinical and process validation batches. The following substantive issues were resolved in the course of the review:

Potency by the OC Assay

The target (b)(4) activity by the OC assay was revised, from ----(b)(4)-----, beginning with ----(b)(4)----- to better accommodate to the target Potency value (500 U/vial) in the DP. This revision resulted in an adjustment in rpFVIII Potency in DP. Therefore, statistical analysis was performed on DP lots that were formulated using the ----(b)(4)----- batches and produced a LSL of ---(b)(4)---- and USL of ---(b)(4)----. The specification is set in accordance with the -----(b)(4)----- of the target potency, which is in the range of ---(b)(4)-----. This is acceptable as it ensures a more stringent control of DP Potency.

Regarding applicability of the method, in the validation of the OC assay for FVIII potency, the assessment of accuracy, range and repeatability did not meet the requirements of ICH Guideline Q2R1 in that an insufficient number of concentrations and samples were used to cover the established range. In addition, the FDA was concerned about the use of the same material as the standard and sample, and the qualification of the positive control. These concerns were satisfactorily addressed with re-validations of the parameters and the submission of data demonstrating parallelism between dilution curves for the references and samples (Amendments 17 and 18).

The approach used in the validation of the OC assay also did not allow the assessment of intermediate precision in a statistically valid manner. The Applicant performed a re-validation of this parameter as recommended by the FDA (Amendment 24). The OC assay is now considered

to be adequately validated and suitable for its intended use as a DP lot release test and as the DP potency assignment assay. In addition, this assay is generally used in clinical laboratories.

Specific Activity

Specific Activity is a calculated value based on the Potency and Protein Concentration values; and is indicative of product purity. Statistical analysis was performed using only the data for those DP lots for which potency was determined against the primary reference standard ---(b)(4)----- . This in-house product-specific standard was implemented at the time of the manufacture of the Phase III Clinical material and was also used in the process validation studies (from -----(b)(4)----- . The specification range was established based on adequate statistical analysis of these historical manufacturing data that fell within a consistent and normally distributed range: 11000 – 18000 U/mg (reported to 2 significant figures). This range is comparable to the ranges for other approved FVIII products (5500-9900 IU/mg for XYNTHA; ADVATE 4000 – 10000 IU/mg for ADVATE; 2600 – 6800 IU/mg for Kogenate FS; and ---(b)(4)---- for Novoeight).

Potency by the CS Assay

A number of deficiencies were identified with the initial validation of the CS assay for potency: the validation of specificity did not account for the effect of excipients; the validation of intermediate precision, repeatability, range and accuracy was performed using the same material as the standard and sample that was circular; the accuracy study did not cover the required --- (b)(4)-- range of the target potency value; and the qualification data for the standard used in the method validation was found insufficient. Per FDA request, the method was re-validated, and the new validation report was submitted in Amendment 29 (24 August 2014).

Although the CS method was re-validated, both the Applicant and the Agency identified issues related to assay variability that appeared to be dependent on the chromogenic reagent kits and reference standards used. The Division of Biological Standards and Quality Control (DBSQC) encountered the variability during in-support testing of the PV batches when different results were obtained using two different kits for the same DP lot. These issues were discussed during the 22 August 2014 teleconference. Baxter acknowledged the shift in the CS values with each change of the reference standard, and dependence of the results on the chromogenic kits. Baxter ascribed this variation to the qualification of previous product-specific reference standards (rpFVIII) directly against WHO *primary* reference standards (human FVIII) where rpFVIII and human FVIII interact differently with the FIXa reagent of the chromogenic kits. For this reason, Baxter qualified an rpFVIII material originating from -----(b)(4)----- as a new product-specific *primary* reference standard for potency. ---(b)(4)----- was qualified in a collaborative study of five laboratories and its potency value was assigned against the WHO 8th International Standard for FVIII concentrate which is of human origin. The correction factor with regard to the previous standards was established for the retrospective analysis of the historical data, and the use of ---(b)(4)---- is expected to mitigate any further shifts with future standards that will be qualified against ---(b)(4)---- (like-versus-like concept).

The correction factor was determined based on the difference between the two potency values (OC/CS ratio) which is specific for each reference standard qualified. When setting the specification range for FVIII Activity by the CS assay, the correction factor was applied to re-

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

If the URL is exceeded, a full investigation will be initiated and conducted by both (b)(4) and Baxter to determine the root cause and the lot’s disposition. The actions will include the enrollment of the affected lot in stability studies under real-time and accelerated storage conditions. The lot will only be released if -----
----- (b)(4) -----
-----, SOP # MF-20-002QA “Disposition and Release of OBI-1” will be revised to describe this additional analysis prior to disposition of the lot.

The final DP Release Specification submitted in Amendment 37 and reproduced in Table 8 is considered adequate to control the identity, purity, potency, and safety of OBIZUR.

EXEMPTION FROM CBER LOT RELEASE

The Laboratories of the Division of Biological Standards and Quality Control (DBSQC) in the Office of Compliance and Biological Quality (OCBQ), CBER, FDA, performed in-support testing of the three PV batches of OBIZUR for the following parameters:

- Appearance pre- and post-reconstitution
- Reconstitution Time –(b)(4)---
- Water Content by ----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- Purity by ----(b)(4)----- and Identity by ----(b)(4)-----
- FVIII Potency by the OC and CS assays
- Endotoxin by the -----(b)(4)-----

With the exception of the CS assay, all methods performed adequately, with all system suitability and assay validity criteria satisfied. The DBSQC results for the three DP lots tested were within the proposed specifications and comparable to the results reported by the Applicant. As discussed above, the potency values measured by the CS assay were variable depending on the kit used for measurement, and did not meet the acceptance criteria on some occasions.

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (8 December 1995), routine lot-by-lot release by CBER is not required for OBIZUR because it is a well-characterized recombinant product. Baxter has demonstrated its ability to adequately control the manufacturing process, and consistently produce product lots of established quality. The in-support testing by CBER/DBSQC confirmed the results of batch analyses for PV lots reported in the BLA and the suitability of critical quality-defining methods for their intended use as lot release specification tests. Thus, exemption of OBIZUR from CBER Lot Release is justified.

CONCLUSION

The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls in the BLA and has adequately addressed the requests from all CMC reviewers in Amendments 17, 21, 24, 29, 37, and 42. The manufacturing process for OBIZUR, Antihemophilic Factor (Recombinant), Porcine Sequence, is considered to be adequately validated at the commercial scale and is sufficiently controlled to ensure consistent manufacture of the commercial product that meets the justified release specifications.

The implemented control strategy for the cell bank system and the developed manufacturing processes for the DS and DP provide acceptable safety margins regarding adventitious agents, as reflected in this document and in the memorandum of Dr. Ze Peng.

The analytical methods for the determination of specification parameters are adequately validated and are suitable for their intended use as lot release tests, as concluded by Drs. Khrenov, Bhattacharyya and Del-Grosso. Dr. Khrenov also concluded that Baxter's program for reference standard qualification and maintenance is acceptable. Two in-house product-specific primary reference standards (potency and quantitative) have been qualified for routine analytical testing of commercial DS and DP.

Thus, the information on Chemistry, Manufacturing, and Controls is sufficient and satisfactory, and I recommend **APPROVAL** of Baxter's BLA for OBIZUR. This recommendation is shared by all members of the review committee.