

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 for BLA (STN 125512/0)
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Through: Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR

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Subject: Final review of the *Analytical Methods* and *Stability* sections in Baxter's original BLA for Antihemophilic Factor (Recombinant), Porcine Sequence

EXECUTIVE SUMMARY

This memorandum summarizes the review of the *Analytical Methods* and *Stability* sections of the original BLA under STN 125512/0 for Antihemophilic Factor (Recombinant), Porcine Sequence. (Applicant – Baxter International, USA; proposed proprietary name – OBIZUR; company code OBI-1)

All analytical methods used for the characterization of the identity, purity, quality and safety of the Drug Substance and Drug Product have been adequately validated to support their intended use in the manufacture of OBIZUR. The design of the stability studies is adequate, and the study results support the proposed shelf-life of 24 months for this product. Thus, the information on analytical methods and stability studies support the approval of the BLA.

BACKGROUND

OBIZUR is a recombinant (r) analogue of porcine Factor VIII (pFVIII). 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 cleaved to the heavy chain (A1-A2-B) and light chain (A3-C1-C2) held together by a metal ion --- (b)(4)----- bridge. In OBIZUR, the B-domain is deleted and replaced with a linker containing the first 12 and the last 12 amino acid residues of the pFVIII B-domain, resulting in a molecule of ---- (b)(4)----- at about 165 kDa.

Porcine FVIII could be active in the human coagulation pathway and has reduced reactivity to inhibitory antibodies against human FVIII. Ipsen's plasma-derived pFVIII (Hyate:C) was licensed to treat hemophilia A patients with inhibitors for over 15 years, until its manufacture was hampered by supply issues related to porcine plasma.

The proposed indication for OBIZUR is for the treatment and prevention of bleeding episodes in adults with acquired hemophilia A.

The drug substance is manufactured at the Baxter facility in ---(b)(4)----- in the form of a

----- (b)(4) -----
-----, where vial filling and lyophilization are performed to manufacture a product at dosage strength of 500 units per vial. The vials are then transported to the Baxter facility in ---(b)(4)----- for final packaging and labeling.

This reviewer participated in the pre-license inspection (PLI) of the ----(b)(4)----- facility on ----(b)(4)-----.

REVIEW SUMMARY

Modules reviewed (including relevant documents supplied in appendices and amendments):

3.2.S.4.2 Analytical Procedures
3.2.S.4.3 Validation of Analytical Procedures
3.2.S.5 Reference Standards or Materials
3.2.S.7 Stability

3.2.P.5.2 Analytical Procedures
3.2.P.5.3 Validation of Analytical Procedures
3.2.P.6 Reference Standards or Materials
3.2.P.8 Stability

Review History

The application was submitted as a rolling BLA beginning with the Non-Clinical modules on 10 October 2013; followed by the CMC Quality and Facility modules on 8 November 2013; and finally the Clinical modules on 25 November 2013. The BLA was reviewed under the Priority Review schedule of the PDUFA V program.

Analytical procedures review issues were discussed with the company during the PLI of the ----(b)(4)----- facility on -----(b)(4)-----.

Information Request (IR) sent on April 4, 2014, included questions regarding analytical procedures. The response to IR was received on April 25, 2014, which was reviewed and deemed adequate. Additional questions on the stability program were raised and resolved around the time of the Late-Cycle Meeting in late August 2014.

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DRUG PRODUCT SPECIFICATION AND ANALYTICAL PROCEDURES

Description of the analytical procedures for the drug product (DP) and their validations are provided in sections 3.2.P.5.2 Analytical Procedures, 3.2.P.5.3 Validation of Analytical Procedures and 3.2.P.6 Reference Standards or Materials, which are reviewed below.

The majority of the methods employed are the same methods as used for testing of (b)(4). For a number of methods, validation was performed for the --(b)(4---) DP in the same study. The review below covers only the methods which are different from the methods used for the (b)(4)- or if supplemental validation is performed.

Compendial methods

1. Appearance

Same as that used for the (b)(4).

2. Reconstitution time

The reconstitution time is determined for the OBIZUR DP following reconstitution with 1 mL of water for injection (WFI) or purified water. The time taken for the contents to dissolve completely based on visual assessment is recorded.

The method is adequate to assess the reconstitution time of OBIZUR DP.

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Table 3. OBIZUR Drug Product Specification

Attribute	Method and Pharmacopeia Reference	Specification
Physical and Chemical	Appearance --(b)(4)---	Pre-reconstitution: white cake Post reconstitution: clear, colorless solution, essentially free of visible particulates
	Reconstitution time	---(b)(4)-----
	----(b)(4)----- -----	---(b)(4)----- -----
	pH ----(b)(4)-----	---(b)(4)----
	Protein Concentration ----(b)(4)-----	---(b)(4)-----
	Water Content ----- (b)(4) -----	---(b)(4)-----
Identity	---(b)(4)---	Corresponds to reference standard
Impurities	----- (b)(4) -----	(b)(4)
	----- (b)(4) -----	(b)(4)
Potency	FVIII Activity by One Stage Coagulation (OSCA)	----(b)(4)-----
	Specific Activity: One Stage U/mg protein	11000 to 18000 U/mg
	FVIII Activity by Chromogenic	Report
Purity and Heterogeneity	----- (b)(4) ----- -----	(b)(4)
	----- (b)(4) ----- -----	(b)(4)
	----- (b)(4) -----	--(b)(4)---
	----- (b)(4) -----	--(b)(4)---
	----- (b)(4) -----	--(b)(4)---
	----- (b)(4) ----- -----	(b)(4)
Safety	Sterility --(b)(4)---	Negative, ----- (b)(4) ----- -----
	Endotoxin --(b)(4)---	----- (b)(4) -----
Excipients	Sodium	----- (b)(4) -----
	Calcium	----- (b)(4) -----
	Citrate	----- (b)(4) -----
	Chloride	----- (b)(4) -----
	Tris	----- (b)(4) -----
	Sucrose	----- (b)(4) -----
	Polysorbate 80	----- (b)(4) -----

The test is performed per ---(b)(4)----- by a contract facility. No validation is required.

The method is adequate to assess -----(b)(4)----- in the OBIZUR DP.

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5. Water Content by --(b)(4)--

The moisture content of lyophilized OBIZUR DP is measured by ----- (b)(4) -----
----- reaction. The moisture content is expressed as % weight of the lyophilized cake
(w/w). The residual moisture content is determined by means of ----- (b)(4) -----
----- according to ---- (b)(4) -----.

Method Validation

The method was validated and the results were submitted in validation reports AMV -RP-
MVR(1)-M002/M008, 112835-RPT and 114328-RPT.

*The initial validation was performed as described in AMV -RP-MVR(1)-M002/M008. The
validation was assessed by the company and concluded to be not compliant with ICH guidelines.
The analysis of AMV -RP-MVR(1)-M002/M008 was provided in 112835-RPT and supplemental
validation results were submitted in 114328-RPT. The validation summary as described below is
derived from all 3 documents.*

The following parameters were validated:

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The method is adequate to assess moisture content in OBIZUR DP.

6. Sterility

This test is performed to confirm the sterility of the final OBIZUR DP, in accordance with the requirements of -----
----- (b)(4) -----.

The test for sterility is used to reveal the presence of viable forms of bacteria and fungi in aseptically filled lyophilized drug product. The sterility of the OBIZUR DP is determined according to ----- (b)(4) -----.

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

Method verification

The method was validated using DP lots ---- (b)(4) ----- and the results were submitted in validation report MMV-RP500-MVR(1)-M002/M004.

The method was verified as it was able to recover all challenge microorganisms spiked in the DP at the concentration of -----(b)(4)----- . The media and microorganisms used for the validation study are listed in Table 4.

Additional studies MMV-GE-IR(1)-M040/M010 were performed to verify container/closure integrity during the sterility test -----(b)(4)----- . The study established that post-exposure of the test equipment to -----(b)(4)----- and its use during the execution of the sterility test method does not impair the ability of the method to recover microbial contamination.

[(b)(4)]

The method is adequate to test sterility of the OBIZUR DP.

7. Endotoxin

This test is performed to evaluate OBIZUR samples for endotoxin. An endotoxin control standard is prepared against a Reference Standard Endotoxin. This control standard is used to prepare a series of dilutions of -----

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

-----.

Method validation

The method was verified for testing the OBIZUR DP and the results are submitted in Validation Report M-2005-029 VR(b). Re-validation report MMV-GE-RR(1)-M010-M020 reviewing the validation of method 3 years after the initial validation was also submitted in the BLA confirming the validated status of the method.

The following parameters were verified:

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The validation summary submitted in section 3.2.P.5.3 incorrectly listed ---(b)(4)----- as the range (clerical error). The values in the actual validation report are correct.

The method verification demonstrated that the Endotoxin procedure is qualified to be used for the release of the OBIZUR DP.

Non-compendial Methods

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9. ---(b)(4)-----

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10. FVIII Activity by One-Stage Coagulation Assay (OSCA)

The same test is used for the (b)(4).

Additional validation was performed for testing the OBIZUR DP by OSCA at the ---(b)(4)----- site. The results of the validation are submitted in the validation report 114393-RPT.

The method was validated using Reference Standard ----(b)(4)----- and DP lot --(b)(4)---.

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The method can be considered as adequately validated for determining the potency of the OBIZUR DP.

11. FVIII Activity by Chromogenic Assay.

The acceptance criterion of the chromogenic assay (CA) in the DP specification is “For Information Only”.

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The chromogenic substrate assay for FVIII activity is based on the -----

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

The test uses the FVIII chromogenic kit (FIXa, FX, and chromogenic substrate reagents) manufactured by --(b)(4)--.

The analytical procedure description in the BLA list “Factor VIII Chromogenic Assay Kit, e.g., --- (b)(4) ---”, which is not correct. It is known that the results of chromogenic assay of the potency of non-plasma derived FVIII products are dependent on the kit used, so the --(b)(4)-- kit should be specifically mentioned in the description. While the initial qualification of the method was performed using the --- (b)(4) --- kit, the information in the BLA needs to be current.

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REFERENCE STANDARDS OR MATERIALS

1. Historical Reference Standards

An overview of the historical reference standards used in the testing and release of the OBIZUR (b)(4) and lyophilized DP, from early product development through the Phase 3 clinical trials, is provided in Figure 9.

The materials selected were required to have sufficient volume of (b)(4)/DP in order to enable its release and characterization testing, enrollment in a minimum of (b)(4) stability testing program, and OBIZUR in-process and release testing of the OBIZUR (b)(4) and DP batches. The reference standards were also used in pharmaceutical development as well as method development, qualification and validation studies (see above). Typically between ----(b)(4)----- vials of the reference standard are generated; a new reference standard was identified when (b)(4) vials of the out-going reference standard remained.

OBIZUR Reference standards are used for both qualitative and quantitative testing. As there is no World Health Organization (WHO) recognized primary standard identical to the

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recombinant porcine FVIII product, quantitative OBIZUR reference standards (in-house reference material) serve as primary reference standards for all attributes tested. Analytical testing utilizes 3 types of reference standards for the analysis of OBIZUR DS and DP:

- OBIZUR Potency Reference Standard, primary -----(b)(4)-----
-----, used only for potency testing);
- OBIZUR Quantitative Reference Standard, primary (lyophilized drug product used for all assays except for potency); and
- OBIZUR Qualitative Reference Standard, secondary (lyophilized drug product used for -----(b)(4)-----).

The initial OBIZUR reference standards -----(b)(4)----- were used during pre-clinical studies. The potency of --(b)(4)-- was assigned against -----(b)(4)----- and using only the Chromogenic assay, and thus assigned a single potency. These two pre-clinical OBIZUR reference materials were used to calibrate the first OBIZUR reference standard used to release the clinical product, -(b)(4)-. The protein concentration and chromogenic potency were assigned against the initial pre-clinical reference standards. In addition, a one-stage potency was also assigned to -(b)(4)- vs the -(b)(4)- reference standard. Subsequent Phase 2 OBIZUR reference standards were calibrated vs the previous OBIZUR reference standard (e.g., the next OBIZUR reference standard-(b)(4)-was calibrated against reference standard -(b)(4)-).

These Reference standards were used during the development stage only, not for methods validation.

All (b)(4) batches selected for use as reference standards in the Phase 2 and 3 studies were manufactured at Baxter -----

The difference between the results obtained by OSCA and CA when measured against a plasma-derived standard is common for recombinant FVIII products, especially B-domain-deleted analogs.

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*All reference standards were characterized with tests used for product release. Starting from ----
--(b)(4)---- additional parameters were characterized for qualitative and quantitative reference
standards, including -----(b)(4)-----
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*The development history for reference standards is well documented and allows traceability of
the current reference standards to the historical reference standards used in the development
process.*

2. Current reference standards for the use in (b)(4) and commercial DP release

Currently three references standards are used for (b)(4) and DP release:

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The use of three standards is appropriate for this product, as the analytical methods used operate at significantly different concentrations, i.e., the use of the quantitative reference standard as potency standard will require dilution with large dilution factors (or multiple dilutions) significantly lowering the accuracy of the assay, and negatively impacting the calibration and qualification of new reference standards.

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The most recent version of stability data reviewed in this section is provided as part of Amendment 29 to the BLA and is based on report SR-181 dated August 14, 2014.

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The complete list of stability lots is presented in Table 6 and methods used for stability testing of DP are presented in Table 7.

Real Time/Real Temperature Stability Studies (5 °C)

Appearance, (b)(4), reconstitution time and identity by --- (b)(4) -- have not shown any statistically significant trends over time at (b)(4) and have remained within specifications across all time-points.

[(b)(4)]

Potency by OSCA was stable for up to --(b)(4)-- when stored at -----(b)(4)----- showed statistically significant downward trends. However, all of the results (including up through ---(b)(4)--- and 24 months available respectively for lots -----(b)(4)----- to date were within specification through the minimum intended 24 month shelf-life. The slopes and regression coefficients of the trend for these two lots were also low. Baxter concluded that these trends are not a stability concern for these two lots.

I find the Baxter conclusion to be scientifically sound and acceptable.

Table 7. DP Stability Test Methods

Assay Type	Test Method	Acceptance Criteria
Appearance	Visual Inspection	General Appearance
(b)(4)	----- (b)(4) -----	--- (b)(4) -----
Water Content	----- (b)(4) -----	--- (b)(4) ----- --- (b)(4) -----
Protein Concentration	--- (b)(4) -----	--- (b)(4) ----- --- (b)(4) ----- --- (b)(4) -----
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FVIII Activity	OSCA	--- (b)(4) -----
--- (b)(4) ---- --- (b)(4) ---- --- (b)(4) ---- --- (b)(4) ----	--- (b)(4) -----	--- (b)(4) ----- --- (b)(4) ----- --- (b)(4) -----
% Purity ---- (b)(4) ----- -----	Purity by ---- (b)(4) -----	---- (b)(4) ----- ---- (b)(4) -----
Sterility	---- (b)(4) -----	Sterile
Endotoxin	----- (b)(4) ----- -----	---- (b)(4) -----
---- (b)(4) -----	--- (b)(4) -----	---- (b)(4) ----- ---- (b)(4) -----
Identity by --- (b)(4) -----	--- (b)(4) -----	Corresponds to reference standard

Cake moisture at 5 °C showed a statistically significant increase over time in all lots tested, but all data met the proposed commercial specification of ----- (b)(4) -----, supporting the proposed shelf-life of 24 months when stored at 5 °C.

The data for lot --- (b)(4) - showed a significantly higher rate of moisture increase over the initial time-points (see Figure 5) but the moisture content levelled at approximately --- (b)(4) --- for all time-points after the 9-month time-point (up to the -- (b)(4) -- time-point). An out-of-trend (OOT) investigation was initiated at the 9-month time-point to determine the root cause for the higher than normal moisture uptake in lot - (b)(4) -. The OOT investigation concluded that the root cause was higher levels of moisture in the rubber stopper batches used in manufacture of the OOT lot than for other lots.

The stability data obtained to date provides a high degree of assurance that future commercial lots will consistently meet the proposed commercial moisture specification of --- (b)(4) --- for a minimum of 24 months.

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Protein concentration (also measured by ---**(b)(4)**----- did not exhibit significant changes. While some statistically significant trends were observed, the magnitude of the changes was low and did not affect conclusion regarding the stability of the samples.

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

---**(b)(4)**--- **% purity** data complied with the specification ---**(b)(4)**--- and no change was observed over time.

Accelerated stability studies ---**(b)(4)**-----

For **Potency by OSCA**, there was no statistically significant change in potency over time. However, there is a visibly observable downward trend for lot --**(b)(4)**--- and the p-value **(b)(4)** and slope ----**(b)(4)**----- for this lot. Factor VIII is known to be sensitive to increased temperatures and therefore the negative trend in potency at elevated temperature conditions is expected.

For **Cake Moisture**, all three lots showed a significant increase over time but all remained within specification limit for a minimum of ----**(b)(4)**----- accelerated condition.

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---(b)(4)----- **purity** showed no change over time for any lots at accelerated conditions and all results remained within the proposed commercial specification.

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2. PHOTOSTABILITY STUDIES.

Photostability studies were conducted at --- (b)(4) ----- to investigate the impact of the exposure to --- (b)(4) ----- light and --- (b)(4) ----- light on the DP and the light protecting property of the secondary packaging. OBIZUR DP lot -- (b)(4) -- (manufactured in December 2011) was selected for the study with exposure taking place between ----- (b)(4) ----- duration).

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No change in results for (b)(4), appearance, reconstitution time or water content are observed for DP fully exposed to the test conditions compared to DP in foil wrapper or packaged vials.

Table 8. Photostability Study: Testing Schedule

Test	Exposed Vials	Foil wrapped Control	Packaged Vials
Water Content	X	X	X
Chromogenic Assay	X	X	X
One-Stage Coagulation Activity	X	X	X
Protein Concentration ---(b)(4)-----	X	X	X
Variant profile ---(b)(4)-----	X	X	X
Appearance	X	X	X
Reconstitution	X	X	X
(b)(4)	X	X	X
% Purity ---(b)(4)-----	X	X	X
Identity ---(b)(4)-----	X	X	X
---(b)(4)-----	X	X	X

Light exposure has no effect on the activity/specific activity of the packaged vials when compared to the foil wrapped control. A loss in OSCA ----(b)(4)----- and chromogenic activity ----(b)(4)----- was observed in the fully exposed vials when compared to the secondary packaging (cardboard box) or foil wrapped control.

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The OBIZUR DP is photosensitive when exposed to extreme light conditions but photo-stability data show that the proposed commercial package (similar to those used in the study) protects the product from degradation caused by this type of light exposure.

3. FORCED DEGRADATION STUDIES

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4. POST-RECONSTITUTION STABILITY STUDIES

Post-reconstitution (in-use) stability studies were carried out on the primary stability lots at the initial, --- (b)(4) ----- time-points and on the PV lots post shelf-life --- (b)(4) -----.

Initially, only the data for the primary stability lots reconstituted at the time of manufacture were submitted. Additional data to demonstrate in-use stability after storage and in-use stability for process validation lots were submitted per FDA request as part of Amendment 29.

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No trends in (b)(4), appearance, -----(b)(4)-----, protein concentration or ---(b)(4)----- for any of the OBIZUR primary stability batch or PV batch samples from three and (b)(4) hours post-reconstitution were observed. -----
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A decrease in OSCA activity was observed for batch (b)(4) over the (b)(4) hours post-reconstitution at the initial time-point, however, this was not observed for this batch at the --- (b)(4)----- time-points. Despite the trend the results were within specification limits.

No adverse trends in OSCA activity other than (b)(4)- at T=0 hours were observed for the primary stability lots or process validation lots following post-reconstitution, and all batches remained within the commercial specification of ----(b)(4)----- following a --- (b)(4)--- post-reconstitution hold time at the --- (b)(4)----- time-point.

No adverse trends in -----(b)(4)-----, protein concentration and --- (b)(4)----- were observed for all lots tested following post-reconstitution and all batches remained within the commercial specification following a (b)(4) hour post-reconstitution hold time.

The data presented demonstrated no significant changes in stability-indicating parameters for up to (b)(4)- after reconstitution for all tested lots, including those at the end of shelf-life and support the company's conclusion that upon reconstitution, the DP is stable for up to three hours at ambient temperature and light conditions.

5. POST APPROVAL STABILITY PROTOCOL

A minimum of one lot of DP will be placed on stability each year that a new commercial GMP batch of OBIZUR DP is released. DP stability will be examined under real-time storage conditions (2 - 8 °C) against the release specification, in accordance with the testing schedule presented (see Table 9).

The stability protocol was modified per FDA request to include more frequent Endotoxin and Sterility testing and to add Container Closure Integrity testing. The request was made as part of the late-cycle meeting package. The changes to the protocol are deemed adequate. The stability protocol presented allows sufficient control of DP stability post-approval.

[(b)(4)]

CONCLUSION

All analytical methods used for the characterization of identity, purity, quality and safety of Drug Substance and Drug Product have been adequately validated to support the control of the quality of the product and its specifications. The company possesses a set of well-characterized reference standards suitable for characterization and commercial release of the ---(b)(4)--- DP. The development history for reference standards is well documented and allows traceability of the current reference standards to the historical reference standards used in the development process.

Stability studies design and execution support the proposed shelf-life of 24 months for OBIZUR Drug Product at 2-8 °C with light protection. Upon reconstitution, the OBIZUR Drug Product is stable for up to three hours at ambient temperature and light conditions.

I recommend approval of the BLA for OBIZUR from the analytical methodology and stability perspective.