

MEMORANDUM



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

TO: Administrative File STN: 125512/0
Antihemophilic Factor (Recombinant), Porcine Sequence (OBI-1)
FROM: Qiao Bobo, Ph.D., Regulatory Officer, CBER/OCBQ/DMPQ/MRBII,
THROUGH: Marion Michaelis, Chief, CBER/OCBQ/DMPQ/MRBII
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OMPT/CBER/OBRR/DH/LH

APPLICANT: Baxter Healthcare Corporation (Baxter) License No. 140

FACILITIES: Baxter -----(b)(4)-----
----- (b)(4) -----
Baxter----- (b)(4) -----
----- (b)(4) -----,
----- (b)(4) -----
----- (b)(4) -----

SUBJECT: Review Memo – Biologics License Application (BLA) for treatment and prevention of bleeding episodes in patients with acquired inhibitory antibodies to human factor VIII (i.e., acquired hemophilia patients)

ACTION DUE DATE: October 25, 2014

RECOMMENDED ACTION:

Approval

REVIEW SUMMARY:

The recommended action noted above is based on:

- Review of DMPQ-related information included in the Biologics License Application (BLA) and its amendments (STN 125512/0).
- The pre-license inspection that was conducted ---(b)(4)----- at Baxter’s -----(b)(4)----- Drug Substance manufacturing facility.

- The pre-license inspection that was conducted -----(b)(4)-----
----- Drug Product manufacturing facility.

Upon review of the original BLA submission, multiple Information Requests were sent to Baxter Healthcare Corporation (Baxter) in December, 2013, January-March, August and September 2014, and teleconferences were conducted to clarify the agency expectations. Baxter submitted numerous amendments in response to DMPQ Information Requests throughout the review cycle with the latest amendment submitted on September 26, 2014. Based on the review of original submission and the amendment submitted on July 20, 2011, I had six additional Information Requests and the responses were acceptable taken together (see **INFORMATION REQUESTS** section for details).

In addition, during the late cycle meeting with Baxter on August 19, 2014, Baxter agreed that -----(b)(4)----- facility is currently used only for the manufacturing of OBI-1. If Baxter decides to introduce other products into this facility after the licensure of OBI-1, an appropriate regulatory submission is required to report the change.

Detailed information related to pre-license inspections is summarized separately in the FDA Form 483 Response Memos and the Establishment Inspection Reports (EIR).

All review issues and inspection issues have been resolved. Therefore, I recommend the approval of Baxter's BLA for Antihemophilic Factor (Recombinant), Porcine Sequence (OBI-1) under STN 125512/0.

ENVIRONMENTAL ANALYSIS:

Baxter requested categorical exclusion from an environmental assessment pursuant to 21 CFR 25.31(c), which applies to a biologic product containing substances that occur naturally in the environment when the introduction of the product does not alter significantly the concentration or distribution of the substances, their metabolites, or degradation products in the environment. The request for categorical exclusion is justified as OBI-1 is a protein-based product that is composed of naturally occurring substances.

Baxter further stated that to Baxter's knowledge, no extraordinary circumstance exists according to 21 CFR 25.15(d).

INTRODUCTION:

Baxter submitted this original BLA for Antihemophilic Factor (Recombinant) Porcine Sequence (OBI-1) under the rolling review agreement, which was based on designated Fast Track status (priority eight months review).

OBI-1 is a purified glycoprotein produced by a genetically baby hamster kidney (BHK) cell line that is extensively characterized. OBI-I is formulated as a sterile, nonpyrogenic,

lyophilized powder preparation. OBI-I will be marketed in single-dose vials packaged into a product kit consisting of ten product vials, ten diluent syringes (approximately 1 mL of sterile Water for Injection in each pre-filled syringe), ten vial adapters with filter, and one package insert.

The proposed indication for OBI-1 is for the treatment and prevention of bleeding episodes in patients with acquired hemophilia A, which is within the scope of the indication approved for the orphan drug designation (#03-1814) for Baxter claiming orphan exception for the PDUFA user fee requirement for this BLA.

PRODUCT DESCRIPTION:

OBI-1 is a purified recombinant porcine factor VIII, B-domain deleted protein with ----(b)(4)----- in the full length heterodimer or single chain. Full length human and porcine factor VIII are synthesized as a single product with the domain structure A1-A2-B-A3-C1-C2. In OBI-1, the porcine factor VIII B-domain has been replaced with a twenty-four amino acid linker. Recombinant porcine factor VIII, B-domain deleted [Antihemophilic Factor (Recombinant), Porcine Sequence], is a glycoprotein that is secreted by genetically engineered baby hamster kidney (BHK) cell line.

OBI-1 drug product is supplied in a 3 mL ----(b)(4)----- glass vial as a white lyophilized product for reconstitution with 1 mL sterile Water for Injection (sWFI) to yield a final potency of 500 units/mL. There is one-dosage strength for this product. Each vial is reconstituted using pre-filled 1 mL sWFI prior to intravenous injection.

The OBI-1 drug product is formulated as a sterile, nonpyrogenic, white, lyophilized powder preparation and is stabilized with a mixture of sugars and salts.

----- (b)(4) -----, sterile filtered and aseptically filled into vials (0.5 mL / vial) prior to lyophilization. No additional components are added to the (b)(4) prior to filling and lyophilization into the drug product vials.

ESTABLISHMENT DESCRIPTION:

The manufacture of OBI-1 (b)(4) is performed at the Baxter -(b)(4)-- facility located in ----(b)(4)----- . Manufacture of OBI-1 drug product is performed by a contract manufacturer,----- (b)(4)----- . The packaging and labeling of final drug product is performed at Baxter ----(b)(4)----- located in --- (b)(4)----- . The diluent is manufactured by ----- (b)(4)-----

Baxter -(b)(4)-- and Baxter -----(b)(4)----- are under the FDA License (b)(4) issued to Baxter Healthcare Corporation (Westlake Village, CA). The FEI # for Baxter, (b)(4), is

---(b)(4)----- . The FEI # for Baxter -----(b)(4)----- . Baxter (b)(4) is not yet an FDA licensed facility; an establishment registration application has been submitted on 26 November 2013 and the application was validated by FDA on 17 December 2013. -----(b)(4)----- is a manufacturer contracted by Baxter Healthcare Corporation to further process the OBI-1 active drug substance into finished OBI-1 drug product. The diluent is manufactured by -----(b)(4)----- . The roles of the six facilities in OBI-1 manufacturing are summarized in **Table 1**.

Table 1. OBI-1 Facility Roles

Site	Roles with regards to OBI-1
Baxter Healthcare Corporation (West Lake Village, CA)	A Baxter division headquarters and the license holder. Location of the Reporting Official on the Blood Establishment
Baxter -----(b)(4)-----	OBI-1 (b)(4) manufacturing facility -----(b)(4)----- .
----- (b)(4) -----	OBI-1 Drug Product manufacturing facility (A Contract Manufacturing Organization for Baxter).
Baxter -----(b)(4)-----	OBI-1 labeling and secondary packaging facility.
----- (b)(4) -----	Sterile Water for Injection, 1 ml Prefilled syringe
----- (b)(4) -----	Sterile Water for Injection, 1 ml Prefilled syringe

Drug Substance Facility – Baxter (b)(4), US

The OBI-1 (b)(4) is manufactured at Baxter Healthcare, -----(b)(4)----- located at -----(b)(4)----- .

There are (b)(4) separate buildings on the site, designated as -----(b)(4)----- .

----- (b)(4) ----- houses a Research and Development, an animal facility, and office space areas. ---(b)(4)--- is not used for any of the activities associated with OBI-1 and is not connected to ---(b)(4)---, which is where all OBI-1 manufacturing and Quality operations take place.

---(b)(4)--- was built with the sole purpose to manufacture OBI-1 and (approximately --- (b)(4)--- is a separate structure which includes the GMP manufacturing area, QC laboratories, warehouse and material management and office space. OBI-1 is the only product made at the (b)(4) facility.

Baxter --(b)(4)- is not yet an FDA licensed facility; an establishment registration application was submitted on 26 November 2013 and the application was validated by the FDA on 17 December 2013.

CBER conducted a pre-licensing inspection (PLI) at Baxter Health Corporation’s ---(b)(4)---- facility during ----(b)(4)------. The pre-license inspection covered Quality, Facility & Equipment, Materials Management, Production, Packaging & Labeling, and Laboratory Controls Systems with respect to the manufacture of OBI-1 drug substance. At the conclusion of the inspection, CBER issued FDA Form 483 with nine observations. Deficiencies were noted in the areas of qualification of bulk drug substance container closure system; deviation management; Qualified Building Management System (QBMS) SOP to manage excessive alarms; QC laboratory SOP related to buffer preparation; review and assessing validation results for laboratory testing procedures; handling -----(b)(4)-----; record keeping for equipment use logs. Baxter (b)(4)-- provided corrective actions to address the FDA Form 483 items. The corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved (see Baxter (b)(4) Pre-License Inspection FDA Form 483 Response Memos for details).

Room Classification

ISO classifications are used for the classified manufacturing environment. **Table 2** shows the area classification where manufacturing operations are carried out. All activities associated with open manipulation of the cell culture inoculation, expansions and harvest, as well as final drug substance fill, are carried out in (b)(4) areas.

[(b)(4)]

Drug Product Facility – -----(b)(4)-----

The -----(b)(4)------. It is a contract manufacturing organization for Baxter’s OBI-1 drug product. It is a multiproduct facility and consists of (b)(4) manufacturing units; -----(b)(4)-----

---(b)(4)---. OBI-1 drug product (DP) is manufactured and packaged in the -----
----- (b)(4)----- facilities are also used for support activities (such as
autoclave) of OBI-1 manufacture.

The facility was last inspected by Team Biologics on ----(b)(4)----- for
manufacturing of -----(b)(4)----- drug substance and drug product
in the ---(b)(4)-- facility and the inspection was classified as, “Voluntary Action Indicated
(VAI).”

CBER conducted a pre-license inspection at Baxter’s contract manufacturer at -----
----- (b)(4)----- . The inspection of the -----
--(b)(4)----- facility covered the manufacturing process for OBI-1 drug product, which
includes -----(b)(4)-----, sterile filtration, aseptic filling, lyophilization and over
sealing. The inspection covered Quality, Facility & Equipment, Materials Management,
Production, and Laboratory Controls Systems with respect to the manufacture of OBI-1
drug product. At the conclusion of the inspection, CBER issued Form FDA 483 with six
observations. Deficiencies were noted in the areas of lyophilization process validation,
environmental monitoring program, shipping procedure/validation, and equipment
calibration. (b)(4) provided corrective actions to address the FDA Form 483 items. The
corrective actions were reviewed and found to be adequate. All inspectional issues are
considered to be satisfactorily resolved (see ---(b)(4)----- Pre-License Inspection FDA
Form 483 Response Memo for details).

The ---(b)(4)-----1 facility comprises an -----(b)(4)-----

----- areas are accessed independently through dedicated changing areas.
In addition, there are ancillary unclassified areas for the inspection of drug product vials,
intermediate controlled temperature storage of the drug product and plant room areas.

All aseptic operations are performed within the aseptic core of the facility with the
exception of the (b)(4) sterilization of filling machine change parts which is performed in
an -----

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

----- environment. The rooms utilized for the manufacture of OBI-1 DP, are detailed in

1 Page Determined to be Not Releasable: (b)(4)

[(b)(4)]

Packaging and Labeling facility - Baxter ----(b)(4)-----

The packaging and labeling of the OBI-1 final drug product is performed at Baxter
----- (b)(4) -----
----- . This facility was last inspected by Team Biologics in ----- (b)(4) -----
----- and the inspection was classified as VAI. Pre-license inspection of Baxter’s -----
(b)(4) ----- facility was waived per SOPP 8410.

The packaging and labeling operation of final product has been validated for a different vial format, but has not been validated for OBI-1, a new vial format (3 ml). In response to Information Request, on May 22, 2014, Baxter submitted summary reports for the engineering run for packing and labeling (VN-OBI1-TestRuns.01) and the ---(b)(4)----- integrity testing feasibility study for OBI-1 (3 ml format) at the Baxter (b)(4) facility (Feasibility Report ---(b)(4)----- (see **February 14, 2014 Information Request, Question 7**). The testing run for labeling and packaging of a total (b)(4) OBI-1 vials was successful and the ---(b)(4)----- integrity feasibility study showed consistent pressure and moisture levels for all (b)(4) measured vials. Baxter also stated that the validation will be performed prior to performing packaging operations for commercial launch.

Baxter stated in an amendment submitted on August 25, 2014, that the identity test is performed at --(b)(4)- before labeling at (b)(4). The identity test post labeling is not performed at the same site as that of the release tests. Baxter will perform post labeling identity testing at the --(b)(4)- facility, with the same validated assay that is conducted pre-labeling at --(b)(4)-- and as described in the BLA (3.2.P.5.2 Analytical Procedures [---(b)(4)---]). Section 3.2.P.3.3 has been revised to describe when sampling will occur for the post labeling identity testing.

Diluent Manufacturing Facilities:

There are two diluent manufacturing facilities and both reference their drug master files for the manufacture of sterile water for inject (sWFI) in 1 ml prefilled syringe. Below is a summary of the information based on FACTS data base search and responses to information requests provided by the firm and the vendors (for details see **February 14, 2014 Information Request, Questions 10 and 12**).

1. -----
 -----(b)(4)-----

(b)(4) diluent (sWFI) has been used for two FDA approved products using the same manufacturing process and the same type of container closure system. In addition, based on information from FACTS, the facility was last inspected by ORA in -----(b)(4)----- with “no actions indicated” (NAI). Pre-license inspection of -----(b)(4)----- facility was waived per SOPP 8410.

2. -----
 -----(b)(4)-----

 -----“Sterile Water for Injection, 1 ml Prefilled syringe”

-(b)(4)- diluent (sWFI) has been used for an FDA approved product using the same manufacturing process and the same type of container closure system. The facility was last inspected by ORA in ----(b)(4)----- and the inspection was classified as VAI. Pre-license inspection of -----(b)(4)----- facility was waived per SOPP 8410.

Based on the information available, we decided that no detailed review of the drug master files and no PLIs are necessary for the diluent manufacturing facilities.

MANUFACTURING PROCESS:

Overview of the Manufacturing Process for Drug Substance

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

 -----.

1 Page Determined to be Not Releasable: (b)(4)

Overview of Manufacturing Process for Drug Product

OBI-1 (b)(4) is further processed at -----(b)(4)----- for filling, lyophilization, capping and inspection. A flow diagram of the drug product manufacturing process is provided, see Figure 2.

The unlabeled vials are then labeled and packaged at Baxter's -(b)(4)- facility.

Figure 2. Overview of the Drug Product Manufacturing Process

[(b)(4)]

Process Validation and Process Control:

Based on the cumulative experience from characterization studies and phase 3 manufacturing history (over (b)(4) batches), the process validation (PV) campaign was design for three consecutive batches at commercial scale at the nominal operating conditions.

The OBI-1 (b)(4) batches (batch numbers -----(b)(4)----- were manufactured at Baxter Healthcare, ----(b)(4)----- from January to April 2012 (see **Table 4**) (formerly ---(b)(4)-----) in accordance with the manufacturing process and the process controls in place at the time of manufacture.

[(b)(4)]

OBI-1 DP is a sterile lyophilized parenteral preparation of recombinant factor VIII with a nominal potency of 500 U/vial. OBI-1 (b)(4) is manufactured, -----

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

-----.

Process development data supports -----

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

-----.

[(b)(4)]

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[(b)(4)]

^a Batch aborted due to a failure with the cap detection system on the filling machine

^b Batch invalidated as it was incubated at the incorrect temperature and failed Growth Promotion testing.

In order to re-qualify the aseptic process, routine process simulation tests representative of the OBI-1 process are carried out ----(b)(4)---- as a minimum, according to the above protocol. Where personnel shifts are in place, each shift is required to participate in process simulations.

During the pre-license inspection, I reviewed a Validation Report entitled -----(b)(4)----
----- Manufacturing Facility Process Simulation Report - 2013” [QAR 14-006]. A total of (b)(4) media simulation batches were filled in 2013 and no contaminant units were found. The process included interventions based on filling room activity history as recorded in log books and the operator training requirements. I also reviewed the growth promotion study of all the media used during the process simulation. No issues were noted.

In addition to qualification of the aseptic manufacturing process and the in-process controls, the sterility of the OBI-1 DP is confirmed at release as part of the drug product specification. Sterility has also been confirmed throughout the proposed shelf-life of the product as part of the stability studies.

SHIPPING STUDIES

Shipping of -----(b)(4)-----

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

-----.

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

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

Information Request Question 3). During the pre-license inspection in ----(b)(4)-----
-----, I noticed that the shipping procedure and validation had not been established or
performed, which resulted in a FDA Form 483 Item #4. In response to the Information
Request and the FDA Form 483 observation, Baxter provided the following information.

Shipping Temperature Study

In the February 28, 2014 submission, Baxter stated that Baxter (b)(4) has previously
validated the method of transport for all -----(b)(4)-----
regulated to maintain shipping temperature of 2-8 °C. Shipping validation is designed to
be product- and route-independent. The transport system is validated. The configuration
is able to hold the specified temperature range. This is valid for all products which are
shipped within the specified temperature range.

The Validation Summary Report for “Shipping Validation ----(b)(4)----- + 2°C to +
8°C” was submitted on August 25, 2014. The ----(b)(4)----- is a cool/heat shipping unit
and is able to maintain shipping temperature within the specified range of 2-8 °C. Basis
for the initial validation was the requirement that the (b)(4)-- used were ----(b)(4)--
certified to ensure sufficient conditioning capacity. (The agreement on the -----
------(b)(4)----- and on the special equipment to be used for such
carriage, known as the -----

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

----- During the installation qualification, the ---(b)(4)----- was checked
prior to loading to verify that the (b)(4) is visually clean and empty, check the temperature
of loading area and the heating-/cooling-unit. During the operation qualification, the
temperature allocation in the empty (b)(4)-- was measured ---(b)(4)-----.
Temperature data were within specified temperature limits of 2-8 °C. During
performance qualification, the temperature allocation in the loaded -(b)(4)- was measured
------(b)(4)----- . Temperature data were within specified temperature limits of 2-8
°C. All tests performed complied with the acceptance criteria as defined in the protocol.

Qualification of Physical Integrity of Shipping Configuration

On August 12, 2014, Baxter submitted a study report to demonstrate the physical
integrity qualification of the commercial shipping configuration. The ---(b)(4)----- tray
filled to maximum capacity represents the worst case configuration due to the greatest
overall product mass as well as minimal amount of void fill material. Each of the
------(b)(4)----- . The tests included ------(b)(4)-
-----tests. Upon completion of
testing, each shipping container was opened and each test product was inspected for
defects including broken vials, scratches, cracks, dislodged caps and any other significant
defects observed. All tests met the acceptance criteria.

Shipping Validation

On August 12, 2014, Baxter also provided one actual shipping test run data with OBI-1 product vials and demonstrated that the (b)(4) is capable of maintaining the specified temperature during the shipping. Baxter expects to perform two more shipments to complete the validation. On September 8, 2014, Baxter submitted additional stability data which included testing outside of shipping/storage temperature at accelerated condition of (b)(4) and showed acceptable drug product out to ---(b)(4)----. Considering (a) Baxter (b)(4) has previously validated the method of transport for all -----(b)(4)----- via ----(b)(4)---- regulated to maintain shipping temperature of 2-8 °C that is product- and route-independent; (b) the simulated physical qualification of the shipping configuration under worst case package capacity; (c) the one actual shipping test run data with OBI-1 product vials and the additional stability data submitted, the response is acceptable without a completed shipping validation with three runs.

CONTAINER/CLOSURE SYSTEM:

The OBI-1 drug product is filled in a -----(b)(4)----- glass vial with a nominal capacity of 3 mL. The fill volume is (b)(4)-. The vial is closed with a 13 mm butyl rubber stopper ----(b)(4)-----, and sealed with a 13 mm aluminum overseal and tamper proof snap-off polypropylene flip top. The vials conform to ---(b)(4)----- requirements for hydrolytic resistance.

The components in the container closure system are listed in **Table 9**:

Table 9 Container Closure Components Used by ----(b)(4)-----

Component	Supplier	Manufacturer	Description
Vials	----(b)(4)---- -----	----- (b)(4) -----	3 mL ----(b)(4)---- Glass Vials
Stopper	----- ----(b)(4)--- -----	----- (b)(4) -----	13 mm, Gray,----- ----- (b)(4) ----- -----
Overseal	----- (b)(4)- -----	----- ---(b)(4)---- -----	13 mm FlipOff Clean Certified Seal (b)(4)

Container Closure Integrity ----- (b)(4) -----

The integrity of the 3 mL (b)(4) vials when sealed with (b)(4) 13 mm closures at (b)(4) was assessed by microbial ingress testing at an external testing house. -----
----- (b)(4) -----
----- . As such, process simulations were performed,

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

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

FACILITY, EQUIPMENT, AND UTILITIES (BAXTER ---(b)(4)-----):

Heating, Ventilating, and Air Conditioning Systems

Baxter stated that the facility Heating Ventilation Air Conditioning (HVAC) system uses design considerations aimed at preventing contamination and cross contamination of the product. The HVAC system provides this control through pressure differentials, air exchanges, and control of particulate level. The dedicated HVAC systems for ---(b)(4)--- manufacturing areas are located on the ----- (b)(4) ----- of the building. Each HVAC system is served by common support utilities and systems (i.e. boilers and chillers). The primary air handling units are comprised of ----- (b)(4) ----- . Baxter stated that the system was validated per an approved validation master plan, and all acceptance criteria were met and documented in the validation report.

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

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

Air flows outward from the higher classified rooms to the corridors or areas of lower classification. The AHU are controlled and monitored by an electronic monitoring system which records and monitors temperature and differential pressure. The AHUs undergo regular inspection and preventive maintenance activities which include filter change, filter integrity testing, and maintenance activities performed according to an approved schedule.

A pressure cascade is maintained from the process room environments within the facility out towards the areas of lower classification to afford protection of the product. Specific parameters are set to control and monitor pressure differentials across various areas such as air locks whereby the pressure cascade is maintained even while in use and there is no risk of overlap between the acceptable ranges of two adjacent classified areas. The area classification is further grouped into three main areas:

Controlled areas are accessed controlled by personnel through security card access system.

The HVAC qualification information was not submitted in the original BLA, but it was reviewed during the pre-license inspection. The installation qualification was performed per ---(b)(4)----- classification requirements. The operation qualification (OQ) and performance qualification (PQ) includes the analysis of air and surface samples for viable microorganisms and air samples for non-viable total particulate samples. The number of samples was selected utilizing ----(b)(4)----. The OQ was performed under -----
------(b)(4)------. The acceptance criteria for non-viable particle count and viable count are consistent with -----
------(b)(4)------. Recertification of the HEPA filters and requalification of the cleanrooms are performed ----(b)(4)----- and are up to date.

Water for Injection System

System Description - Water for Injection (WFI) is a validated system used in the manufacturing facility for column rinsing prior to sanitization, facility and equipment cleaning, generation of clean steam for the autoclave, and water generator for the parts washer. The WFI system is designed to produce water at the points of use, meeting or exceeding the -----(b)(4)----- for Water for Injection. The water purification and WFI systems are continuously monitored and equipped with independent alarm systems. The system is composed of -----
------(b)(4)-----
-----.

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

-----.

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

Computer Systems:

Standalone computerized systems (see **Table 16**) are validated using the -----
----- (b)(4) -----
----- . Table 15 shows the qualification/validation activities performed on the
standalone computerized systems. The “X” denotes that the qualification was performed.
No issues related to computer system validation were noted during the pre-license
inspection.

[(b)(4)]

Equipment

Major Process Equipment

The manufacturing process is performed in a product-dedicated suite using product
dedicated equipment. **Table 17** shows the list of major process equipment used in the
manufacture of OBI-1 drug substance process. In addition to the major process
equipment, the OBI-1 drug substance manufacturing process utilizes disposable
technology which includes ----- (b)(4) -----.

Table 17. Drug Substance Major Process Equipment

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CONTAMINATION AND CROSS CONTAMINATION CONTROL (BAXTER (b)(4)--, US):

Facility Cleaning

Procedures are in place for cleaning, disinfecting room and equipment surfaces, sanitization of all drains in the GMP Manufacturing suites -----

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

-----.

Cleaning agents, e.g. Water for Injection (WFI) and disinfectants, are used as an additional step to assist in maintaining the microbiological status of the area. Disinfectants used are fully evaluated according to approved procedures and in compliance with ---(b)(4)----- and other applicable standards.

During the pre-license inspection, I reviewed the facility cleaning procedure and the disinfectant effectiveness study performed by ---(b)(4)--- based on ---(b)(4)--- for the (b)(4) cleaning reagents: -----(b)(4)-----, ----(b)(4)----- performed using -----

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

-----.

Control of Material and Personnel Flow

Baxter stated that the access to the manufacturing suites, restricted to authorized personnel, was designed to enable efficient cGMP operation providing for control of personnel and materials, segregation of product and processes to enable effective manufacture of product. The personnel, material and product flows along with the process and facility are designed to reduce the risk of viral and bacterial contamination.

Manufacturing supplies enter into the facility through the dedicated ---(b)(4)--- loading dock. Materials are transferred to the warehouse/manufacturing material pass through area for cleaning and surface decontamination.

Personnel gowning requirements per room are in place to minimize the risk of contaminants entering the clean room environment. Key card access is required for entry into gowning area. Personnel flow in the manufacturing suite is designed to reduce the risk of viral and bacterial contamination. Material and waste flow is designed to be separated by entry and exit corridors.

1 Page Determined to be Not Releasable: (b)(4)

Environmental Monitoring

Environmental monitoring includes segregated functions by area/room, and air classifications established for each manufacturing space based on the manufacturing step(s) performed.

The Environmental Monitoring Performance Qualification is described in the PQ portion of HVAC Validation (**Heating, Ventilating, and Air Conditioning Systems** section).

The environmental monitoring program is performed -----(b)(4)----- sampling schedule (i.e., -----(b)(4)-----), which includes (b)(4) air sampling sites and (b)(4) surface sampling sites. A total of (b)(4) environmental monitoring samples are processed ----(b)(4)----. Action Limits were established based on -----(b)(4)-----.

During the pre-license inspection, I reviewed the environmental monitoring trending data for 2013 and it showed an overall of 0.1% excursion rate. Excursions were investigated and impact was evaluated. No major issues were noted.

FACILITY, EQUIPMENT, AND UTILITIES ----(b)(4)-----):

Heating, Ventilating, and Air Conditioning Systems

Three separate Air Handling Units (AHU) are installed at the ----(b)(4)---- Facility at the ----(b)(4)----- manufacturing facility, to supply and extract air from the various rooms within the facility.

A dedicated Building Management System (BMS) controls the HVAC systems. Critical parameters associated with the operation of the HVAC system are monitored by a Facility Monitoring System (FMS).

since the original qualification, this minimum requirement for future qualification is acceptable.

Water Systems

There are inconsistencies between the information found in the original BLA submission and information provided during the pre-license inspection.

In the original BLA, it stated “aliquoted WFI is obtained from site manufacturing units for the cleaning.” During the pre-license inspection, I found that the sterile WFI is purchased from a vendor and used for cleaning of (b)(4) areas, and site WFI is used for cleaning of (b)(4) areas of the ---(b)(4)----- facility.

The original BLA did not include the pure steam system in -----(b)(4)----- that is used for -----(b)(4)-----.

The following information is the correct version based on what is collected during the pre-license inspection.

Deionized Water

Within the -(b)(4)- facility, De-ionized Water (DIW) is used to generate ---(b)(4)--- for the (b)(4) sterilization of -----(b)(4)-----.
DIW is generated in -----(b)(4)-----.

Water For Injection

Externally Sourced Sterile Water

Sterile Water is purchased from an external vendor to meet a required specification (including (b)(4) testing for sterility) for the cleaning of all (b)(4) areas in the ---(b)(4)----- facility, including the aseptic filling room.

Site Sourced Water For Injection

Water for Injection (WFI) is not used in the formulation of OBI-1 drug product, cleaning of product contact equipment, or cleaning of container closure components. The -----(b)(4)----- facility does not have a dedicated WFI system. WFI is obtained from the (b)(4) facility for the following uses:

- For cleaning of -----(b)(4)-----.
- To feed to the ---(b)(4)----- clean steam generator used in the -----(b)(4)-----.

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

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

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

Computer systems:

Standalone computerized systems are validated using the -----(b)(4)----- which complies with -----(b)(4)----- (the same approach used for equipment). **Table 18** shows the qualification/validation activities performed on the standalone computerized systems. The “X” denotes that the qualification was performed. The documents for the major computer systems were reviewed during the pre-license inspection and no issues were found.

[(b)(4)]

Equipment

Major Process Equipment

4 Pages Determined to be Not Releasable: (b)(4)

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

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

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

Cleaning Agent Efficacy

Cleaning agents (WFI, detergent, sterile deionized water and disinfectants) are used as an additional step to assist in maintaining the microbiological status of the area.

Baxter stated that disinfectants used within the production areas are fully evaluated according to approved procedures and in compliance with ~~---(b)(4)---~~ and other applicable standards.

Cleaning agent efficacy for product contact equipment is confirmed during the associated cleaning validation activities discussed in this section.

Equipment Cleaning - Procedures and Validation

Equipment Cleaning Process

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

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

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

.

1 Page Determined to be Not Releasable: (b)(4)

[(b)(4)]

Extra monitoring may be performed when required, e.g. in response to unplanned events which may have compromised cleanliness levels or as part of investigations.

During the inspection, it is clarified that “when area is operational” means when area is not shutdown.

Viable Environmental Monitoring is performed to provide on-going evidence that the manufacturing areas are operating in a state of microbial control; assess conformance with specified clean area classifications, and ensure effectiveness of the cleaning and sanitization program. Viable environmental monitoring utilizes contact plates, swabbing, active air sampling and settling plates. Non-Viable Particle Monitoring is required in the ---(b)(4)----- Production Facility to demonstrate that the facility continues to comply with appropriate (b)(4) standards and (b)(4) guidelines. Action Limits were established based on -----(b)(4)----- . During the inspection, I reviewed the environmental monitoring report for January 2012-March 2014, and noted some excursions in three short periods. Overall, the EM trending data for this period showed an overall of 0.9% excursion rate. Excursions were investigated and impact was evaluated. No major issues were noted.

Also, during the pre-license inspection, I noticed that the Laminar Flow Cabinet that provides (b)(4) quality air for ----(b)(4)----- was monitored under (b)(4) specifications for viable counts. The -----(b)(4)-----, so the same environmental standards should be maintained when open manipulations are involved (FDA Form 483 Item #2a). (b)(4) proposed that they monitored the Laminar Flow Cabinet under (b)(4) condition for viable counts and remain (b)(4) condition for non-viable counts (Exhibit#QB-01). Considering the ----(b)(4)----- will the sterile filtered ----(b)(4)----- prior to filling, I accepted the proposal with the expectation that the data collected will be evaluated for setting future specifications for further improvement.

Furthermore, during the pre-license inspection, I noticed that the no samples were taken inside of the rapid pass through chamber which is designed to operate in conjunction with a -----(b)(4)----- and is used to transition materials and equipment into the ----(b)(4)----- area. The rapid path through chamber is located between (b)(4) filling area and the (b)(4) component transfer area and has a validated-- (b)(4)-----

------(b)(4)----- cycle. I pointed out that in addition to validation, an environmental monitoring program must be implemented to detect malfunctions of the system or the presence of adventitious contamination within the chamber (FDA Form 483 Item #2b). In response to the FDA Form 483 Item #2b, --(b)(4)- has implemented a procedure to include the viable environmental monitoring of the pass through chamber -----(b)(4)----- as part of the component transfer monitoring in Component Transfer Room -----(b)(4)-----, upon the completion of all batch related component transfer activities. In addition to the monitoring being done during transfer activities, surface monitoring of the base of the chamber via a contact plate is also implemented during the (b)(4) non-batch environmental monitoring screening. The response is acceptable.

Computer Systems

Standalone computerized systems (see Table 2) are validated using the -----(b)(4)----- approach which complies with -----(b)(4)----- (the same approach used for equipment). **Table 22** shows the qualification/validation activities performed on the standalone computerized systems. The “X” denotes that the qualification was performed.

Table 22 - Computerized Systems Qualification / Validation Status

[(b)(4)]

REVIEW QUESTIONS AND COMMENTS:

Please note, in this sections, the table numbers restart at Table 1 for each Information Request.

December 19, 2013 Information Request

On December 19, 2013, an Information Request from DMPQ was forwarded to Baxter by the RPM, and the response was received on December 27, 2013. DMPQ questions (in

bold) and comments (in bold and italic) and Baxter responses (in plain text) are outlined below.

1. **Regarding your drug product manufacturing facility (----(b)(4)-----facility),**
 - a. **Please list in detail the difference and similarities between the manufacturing of the FDA approved product --(b)(4)-- and the proposed drug product including, but not limited to facility, rooms and equipment used, manufacturing process, container-closure system, validation approach.**
 - b. **Is the establishment performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change)? This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.**
 - c. **Is the manufacturing process is significantly different (new production methods, specialized equipment or facilities) from that of --(b)(4)-- produced by the establishment.**
 - d. **In Section 3.2.P.1.1, Table 1, both the ----(b)(4)----- facility and the Baxter -----(b)(4)----- facility have 100% visual inspection, vial labeling and secondary packaging responsibilities. Please clarify.**

Baxter Response Summary to Questions 1a, 1b and 1c: --(b)(4)-- (FDA approved product) and OBI-1 (Antihemophilic Factor (Recombinant), Porcine Sequence) Drug Products are both manufactured by -----(b)(4)----- at the manufacturing site in -----(b)(4)----- drug substance and drug product are manufactured in the (b)(4)- facility, which is dedicated to the manufacture of this product. OBI-1 is manufactured in the ---(b)(4)----- facility.

While the location, facility designs and operating principles (dedicated vs. multi-product) differ, the Pharmaceutical Quality Systems applied to both products are identical. This includes facility and equipment qualification, validation approaches and manufacturing process control strategies (definition and application of critical control parameters). A more detailed breakdown comparing the two products is provided in **Table 1**.

In addition to the similarities mentioned above, the personnel executing the manufacturing, testing and controls are the same. All manufacturing support activities (testing, validation and commissioning and qualification) are done by the same departments/personnel. For aseptic manufacturing, the oversight of the two facilities is the same while the operators are dedicated or shared, primarily driven by the type of training completed.

Both facilities were inspected by -----(b)(4)----- and were found to be satisfactory with the issuance of a GMP certificate.

[(b)(4)]

Baxter stated that regarding OBI-1 manufacturing process and facility ----(b)(4)-----
-----, no significant changes were made to the facility, location of activities, or
manufacturing process since the time of the submission of the application. No new
products have been introduced nor have any areas, which were previous described as
dedicated, been converted to multi- product manufacturing.

The application describes that the following products are manufactured in ----(b)(4)---
----- facility: OBI-1, -----(b)(4)----- and
investigational -----(b)(4)----- . At this time,
investigational (b)(4) is no longer manufactured in the facility and there is no
intention to do so going forward as the project has been cancelled.

***DMPQ Comment: The purpose of this question is to collect enough information to
determine whether a pre-license inspection waiver can be granted to this facility.***

Base on the information provided, the current FDA licensed product is manufactured in a different suite than OBI-I, therefore, an inspection is needed for (b)(4), the drug product manufacturing facility located in ---(b)(4)-----.

Baxter Response to Question 1d: both the ----(b)(4)----- facility and the Baxter ----(b)(4)----- facility were listed in Section 3.2.P.1.1, Table 1, as alternate sites for 100% visual inspection, vial labeling, and packaging responsibilities. The Baxter ----(b)(4)----- facility will be the site responsible for these activities for OBI-1 commercial manufacturing.

DMPQ Comment: In addition, Baxter stated in its February 28 response to February 14, 2014 Information Request question 7, ----(b)(4)----- facility will not have the necessary equipment upgrades to perform this work and will not be performing labeling and secondary packaging for commercial production. The response is acceptable.

- 2. Regarding your secondary packaging facility in (b)(4), the firm information in your submission is different than the firm information in the (b)(4) establishment inspection report (EIR) (see below). If they are the same firm, please explain the differences in the record.**

Firm information in (b)(4) EIR:

----(b)(4)-----
Baxter Healthcare Corporation- ----(b)(4)-----
-----**(b)(4)**-----
-----**(b)(4)**-----

Information provided in the submission:

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

Baxter Response: Both of these addresses are for the same firm and are referred to as Baxter -----**(b)(4)**-----). The street address listed in the EIR is the legal address and the headquarter address of Baxter (b)(4), the EIR covers the licensed facilities for Baxter (b)(4), including the Baxter (b)(4) facility at ---**(b)(4)**----. The street address included in the submission is more specific for the OBI-1 packaging building, which is within -----**(b)(4)**-----). While they are two different street addresses in ----**(b)(4)**-----, the company is one and the same- Baxter**(b)(4)**.

DMPQ Comment: *The response is acceptable.*

3. Please clarify the relationships among Baxter Healthcare Corporation, Baxter -----(b)(4)-----.

Baxter Response: Baxter (b)(4) and Baxter -----(b)(4)----- are under the FDA License (b)(4) issued to Baxter Healthcare Corporation (Westlake Village, CA). ---(b)(4)----- is a manufacturer contracted by Baxter Healthcare Corporation to further process the OBI-1 active drug substance into finished OBI-1 drug product. The roles of the 4 facilities in OBI-1 manufacturing are summarized in **Table 2**.

Table 2. OBI-1 Facility Roles

Site	Roles with regards to OBI-1
Baxter Healthcare Corporation (West Lake Village, CA)	A Baxter division headquarters and the license holder. Location of the Reporting Official on the Blood Establishment Registration
Baxter -----(b)(4)-----	OBI-1 (b)(4) manufacturing facility ----- (b)(4) -----.
----- (b)(4) -----	----- (b)(4) -----.
Baxter ----- (b)(4) ----- -----	----- (b)(4) -----.

DMPQ Comment: *The response is acceptable.*

4. Please submit a request for Categorical Exclusion with the basis as outlined in 21 CR Part 25.31(a), (b) or (c).

Baxter Response: A request for Categorical Exclusion was submitted in the original submission, Sequence 0000. Please refer to Section 1.12.14 Environmental Analysis. The request for exclusion was based on 21CFR part 25.31 (j), due to marketing of OBI-1 as a biologic product for transfusable human blood or blood components and plasma.

DMPQ Comment: *The request for exclusion was based on 21CFR part 25.31 (j), is not justified because OBI-1 is not a product for transfusable human blood or blood components and plasma. In response to February 14, 2014 Question 9, Baxter resubmitted the request for Category Exclusion based on 21CFR part 25.31 (c) and 21CFR part 25.15(d) on March 28, 2014 and was acceptable.*

5. Please provide the FDA license numbers for Baxter (b)(4) and Baxter -----(b)(4)-----.

Baxter Response: The FEI # for Baxter, -----(b)(4)-----
Baxter -----(b)(4)-----. These facilities are under the FDA

License (b)(4) issued to Baxter Healthcare Corporation (Westlake Village, CA). Baxter (b)(4) is not yet an FDA licensed facility; an establishment registration application has been submitted on 26 November 2013 and the application was validated by FDA on 17 December 2013.

DMPQ Comment: Since Baxter (b)(4) was newly acquired by Baxter, I was not sure if Baxter's license already included the (b)(4) facility. I asked the Product Reviewer/Chair of this file about this. The Product Reviewer/Chair was not sure and suggested that I asked the firm to get the answer. The response is acceptable.

January 14, 2014 Information Request

On January 14, 2014, an Information Request from DMPQ was forwarded to Baxter by the RPM, and the response was received on January 16, 2014. DMPQ questions (in bold) and comments (in bold and italic) and Baxter responses (in plain text) are outlined below.

- 1. Please verify whether the (b)(4) facility in ----(b)(4)----- for manufacturing of the drug product for OBI-1 (BLA 125512/0) is the same manufacturing facility and same FEI as for the BLA STN -----(b)(4)----- . Please state the basis for the revocation action.**

Baxter Response: The facilities (equipment and manufacturing rooms in (b)(4)-- used to make the ----(b)(4)----- drug substance and drug product were decommissioned following the announcement of the cessation of the manufacturing. Following the demolition activities associated with the ceasing of (b)(4) manufacturing, an area of (b)(4) (not associated with (b)(4)- was developed for the manufacture of OBI-1 (reference is made to BLA 3.2.P.2.3 --- (b)(4)----- facility changes, page 29).

The 2004 (b)(4) Annual Report (AR), which was submitted by the license holder (b)(4) (US license (b)(4)). A copy of the Annual Report was attached in the submission. The AR includes the rationale regarding (b)(4) decision to discontinue (b)(4)- and the letter notifying FDA (see Attachment 3 therein). Baxter confirmed that regulatory action (revocation) was not taken by FDA related to this manufacturing license.

The FEI that was assigned to -----
----- (b)(4)----- which is the same number assigned today for ----- (b)(4)-----.

DMPQ Comment: The response is acceptable.

February 14, 2014 Information Request

On February 14, 2014, an Information Request from DMPQ was forwarded to Baxter,

and the responses were received on February 19, February 21, February 28, May 22, August 12, August 25, September 8, September 19 and September 26, 2014. DMPQ questions (in bold) and comments (in bold and italic) and Baxter responses (in plain text) are outlined below.

1. Please provide data or justification for the hold times established for the Drug Substance intermediates.

Baxter Response Summary: To clarify, the OBI-1 (b)(4) manufacturing process does not have distinct process intermediates per the ICH Q5C definition. However, there are -----
----- (b)(4) -----
----- described in **Table 1** and occurs at (b)(4). Both maximum and minimum hold times have been established based upon laboratory studies.

[(b)(4)]

Data to support the maximum hold times has been obtained using representative intermediate materials taken from GMP manufacturing batches, holding them at -----
----- (b)(4) -----
-----.

Data to support minimum (b)(4) hold times have been based upon evaluation of the ----(b)(4)-----.

DMPQ Comment: Baxter provided detailed data supporting the (b)(4) hold steps listed in the table above. The response is acceptable.

2. Please provide a summary of cleaning validation performed for your product contact equipment used during the manufacturing of the Drug Substance including cleaning method, soil used, justification for the soil used, acceptance criteria, justification for the acceptance criteria used, results and conclusion.

Baxter Response: Baxter (b)(4)-- is a single product manufacturing site. The majority of the product contact components are disposable. In addition, resins are

disposed of -----(b)(4)----- are not reused batch to batch. The cleaning method(s) for the non-disposable product contact equipment is provided in **Table 2**. During cleaning validation testing, the equipment was soiled during the corresponding manufacturing process, see **Table 2**. If required, the equipment could be artificially soiled with process soils in a representative way.

[(b)(4)]

Summary of Shipping Validation for (b)(4) (Baxter ----(b)(4)---- to DP Site (-----
(b)(4)-----)

Drug substance shipping was initially validated through two studies. The first study challenged the temperature during shipping by ensuring temperatures were maintained in the drug substance container under worst case simulated conditions. The second study examined historical shipping data to evaluate shipping duration, received condition, post- shipment bioburden, and temperature data. Both studies were successfully completed.

In addition, a supplemental validation protocol was generated and initiated (currently under execution) to qualify the thermal performance associated with the (b)(4) temperature controlled shipment --- (b)(4) -- of OBI-1 (b)(4) from Baxter ----- (b)(4) -----, using the ----- (b)(4) ----- . The shipping validation report was submitted later on August 25, 2014 and was acceptable. (See Review Comment on the Validation Report).

Summary of Shipping Validation for DP Manufacturing Site ----(b)(4)-----
to Final Packaing Site (Baxter (b)(4))

Baxter (b)(4) has previously validated the method of transport for ----- (b)(4) ----- via --- (b)(4) --- regulated to maintain shipping temperature of 2-8 °C. Shipping validation is designed to be product- and route-independent. The transport system is validated. The configuration is able to hold the specified temperature range. This is valid for all products which are shipped within the specified temperature range. The --- (b)(4) ----- is a cool/heat shipping unit and is able to maintain shipping temperature within the specified range of 2-8 °C.

Additionally, Baxter assessed the physical protection in the proposed shipping configuration under simulated laboratory conditions: ----- (b)(4) ----- for empty vials. The results met the qualification requirements and the report was submitted on August 12, 2014.

On August 12, 2014, Baxter submitted the interim validation report for the first test shipment (took place from May 16th to May 19th, 2014) performed with OBI-1 product vials (3ml format) from (b)(4) facility --- (b)(4) ----- to Baxter (b)(4)- facility. Temperature during (b)(4) shipment was within specified temperature range of 2-8°C.

On September 8, 2014, Baxter submitted additional stability data which included testing outside of shipping/storage temperature at accelerated condition of (b)(4) and showed acceptable drug product out to (b)(4) months.

DMPQ Comment:

*Regarding the shipping of (b)(4) from Baxter's ---(b)(4)----- site to ----(b)(4)-----
----- site, the validation protocol and report was submitted on August 25,
2014. Baxter performed three actual production shipments (maximum and
minimum loads) ranged from November 2013 to June 2014, which covers winter
and summer seasons. All TempTale reading were well inside the desired
acceptance limits ----(b)(4)----- . The response is acceptable.*

*Regarding filled Drug Product shipping from ----(b)(4)----- facility to Baxter
----- (b)(4)----- site, the shipping procedure and validation had not been
established or performed during the pre-license inspection, which resulted in FDA
Form 483 Item #4. In response to the FDA Form 483Item #4, on August 12 and
August 25, 2014, Baxter provided simulated shipping test data to demonstrate the
physical qualification of the commercial shipping configuration. The (b)(4)
(b)(4)--- tray filled to maximum capacity represents the worst case configuration
due to the greatest overall product mass as well as minimal amount of void fill
material. Each of the (b)(4)-- trays held (b)(4) units for a total of (b)(4)----. The
tests included -----
----- (b)(4)-----
----- product was inspected for defects including broken vials, scratches, cracks,
dislodged caps and any other significant defects observed. All qualification
requirements were met. Baxter also provided one actual shipping test run with
OBI-1 product vials and demonstrated that the (b)(4) is capable of maintaining the
specified temperature during the shipping. Baxter expects to perform two more
shipments to complete the validation. On September 8, 2014, Baxter submitted
additional stability data which included testing outside of shipping/storage
temperature at accelerated condition of (b)(4) and showed acceptable drug product
out to ---(b)(4)--. Considering (a) Baxter (b)(4) has previously validated the
method of transport for -----(b)(4)----- regulated to
maintain shipping temperature of 2-8 °C that is product- and route-independent;
(b) the simulated physical qualification of the shipping configuration under worst
case package capacity; (c) the one actual shipping test run data with OBI-1 product
vials; and (d) the additional stability data submitted, the response is acceptable
without a completed shipping validation with three runs.*

- 4. Please provide a summary of the validation and the validation report for the lyophilizer used for manufacturing of OBI-1 final product.**

Baxter Response: Baxter submitted multiple amendments in response to this question and follow up questions. The amendments were received February 28, May 22, August 12, August 25, and September 19, 2014. The responses are summarized in the reviewer comments section.

DMPQ Comment:

Lyophilizer qualification information was provided upon Information Request (February 14, 2014 Information Request Question 4) on February 28, 2014, which included the temperature mapping of the empty chamber. -----

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

----- Baxter’s empty chamber temperature mapping strategy and results were acceptable. However, no product temperature mapping and extended sampling were data were provided in this submission (March 19, 2014 Information Request Questions 1-6).

Extended Sampling Issue:

In response to March 19, 2014 Information Request, Baxter provided more data related to extended sampling on April 7, 2014, but the extended sampling tests was only performed for potency and other product specific tests, no data related to residual moisture level and reconstitution time were provided (August 14, 2014 Information Request Question 2).

On August 25, 2014, in response to August 14, 2014 Information Request Question 2, Baxter submitted additional information for residual moisture testing data for a total of (b)(4) OBI-1 buffer samples in relation to the vial location in the lyophilizer demonstrated consistent residual moisture level throughout the lyophilizer chamber. Even though reconstitution time was not evaluated within the lyophilizer development or mapping studies, it has also been consistent over the (b)(4) lots. The reconstitution time results for all (b)(4) lots were provided in detail in the submission. In summary, of all the lots tested, the maximum reconstitution time is 14 sec, and minimum reconstitution time is 5 sec, and the mean is 8 sec. The response regarding the extended sampling questions is considered acceptable based on the totality of the historical data.

Product Temperature Mapping Issue:

During the pre-license inspection, after multiple discussions with (b)(4) regarding historical data, the remaining issue for the lyophilization qualification was that the product temperature mapping had not been performed on the freeze dryer, which resulted in an FDA Form 483 Item #1 – “Validation of the lyophilization process in the (b)(4) Freeze Dryer (Plant Number (b)(4)) is not adequate in that no product temperature mapping was performed.”

On August 12, 2014, Baxter/(b)(4) submitted a lyophilizer validation report including product temperature mapping and the data is summarized below.

(b)(4) locations ---(b)(4)--- on each of the (b)(4) shelves were monitored using -----(b)(4)-----

for the manufacturing of OBI-1. If Baxter decides to introduce other products into this facility after the licensure of OBI-1, an appropriate regulatory submission is required to report the change. Baxter agreed.

7. Please provide a summary of validation or qualification performed for visual inspection, labeling and packaging process performed at the Baxter -----(b)(4)----- site -----(b)(4)----- and the ----(b)(4)----- site if applicable.

Baxter Response (Submitted February 28, 2014):

Answer Related to ---(b)(4)-----

The original 3.2.P.3.1 section listed ----(b)(4)----- as responsible for performing labeling and secondary packaging for the OBI-1 drug product, in addition to Baxter (b)(4). However, ----(b)(4)----- will not have the necessary equipment upgrades to perform this work and will not be performing labeling and secondary packaging for commercial production. Therefore, an amendment to section 3.2.P.3.1 is included in this submission to remove the packaging and labeling responsibilities for -----(b)(4)-----.

In regards to visual inspection, the OBI-1 drug product 100% visual inspection is a manual method and is not automated. The qualification process at ----(b)(4)----- comprises the following:

All operators that perform vial inspection have an initial visual acuity test followed by further periodic --(b)(4)-- visual acuity tests. Any failures are reported to supervision.

All inspection processes are based on a site standard process for commonality across site: Initial Inspection of FD vials is based on a defined training package and standard operating procedure.

Main points for this process:

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

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

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

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

Baxter Answer Related to Baxter (b)(4):

The Baxter (b)(4) establishment will be performing packaging operations in the existing and licensed area using existing equipment. OBI-1 product packaging will be incorporated in the existing packaging process and included in the relevant SOPs. No new equipment and/or processes are used for packaging of OBI-1 product.

1. 100% Visual Inspection is performed with the semi-automated visual inspection line for lyophilized products. The semi-automated inspection consists of operators in front of a special lighted cabinets with the vials transported via conveyor belt. This existing semi-automated visual inspection line is validated and used for different vial formats and lyophilized products currently produced at Baxter -----
 -----(b)(4)----- . The operators who are performing the visual inspections are trained and qualified. For OBI-1 a new vial format (3 mL) will be validated for this inspection line. In place are procedures that outline 100% Visual Inspection, as well as the defect catalog and action limits in the Visual Inspection for lyophilized products.
2. After visual inspection, vial integrity testing is performed by a 100% verification of the ---(b)(4)----- in the vials using the validated -----(b)(4)----- system. Vial Integrity testing is already routinely performed for different vial formats and lyophilized products currently produced at Baxter -----(b)(4)-----
 ----- . For OBI-1, the vial format (3 mL) will be validated.
3. After vial integrity testing, labeling and packaging operations are performed. All requested materials according to the approved bill of material are brought to the defined labeling and packaging area. All materials are 100% verified by bar code scanning before or during the process steps. The printing of lot specific data and labeling of product vials is performed with validated equipment --- (b)(4) --- . The printing of lot specific data on unit carton is performed with validated equipment --- (b)(4) --- . The labeled containers are manually placed in the prepared and labeled product boxes with all required components.
 According to designated procedures, counting and reconciliation for all packaging components has to be performed by exact number. The documentation has to be executed in the Batch Record of the specific work order. If differences in reconciliation occur, a 100% re-check has to be performed to assure the presence of each component. The finished product is stored at 2-8°C.
 All additional validation work due to the 3 mL vial size (including visual inspection and vial integrity testing) will be performed prior to performing packaging operations for commercial launch.

Baxter Response (Submitted May 22, 2014):

Baxter submitted summary reports for the engineering run for packing and labeling (VN-OBI1-TestRuns.01) and the ---(b)(4)--- integrity testing feasibility study for OBI-1 (3 ml format) at the Baxter (b)(4) facility (Feasibility Report ---(b)(4)-----).

DMPQ Comment: I indicated to Baxter that the initial response received in February was not adequate because there should at least be a testing run for the new 3 ml vial format for labeling and packing. So on May, 22, 2014, Baxter submitted the reports for a testing engineer run and the ---(b)(4)--- integrity feasibility study. The testing run for labeling and packaging of a total (b)(4) OBI-1 vials was successful and the --(b)(4)--- integrity feasibility study showed consistent ----(b)(4)----- levels for all (b)(4) measured vials. In addition, Baxter stated that the packaging and labeling line will be validated prior to commercial launch of OBI-1. The response is acceptable for vial integrity testing, packing and labeling operation, but not for the visual inspection portion of it.

During the late cycle meeting, I stated “The semi-automatic Visual Inspection process for a new vial format would require substantially more data to support its approval. You have a validated manual Visual Inspection process at (b)(4)----- facility. For the purpose of the BLA, please clarify whether the Visual Inspection of lyophilized vial will be performed manually at ----(b)(4)----- facility or semiautomatically at Baxter’s (b)(4) facility. Please follow up on Question 7 in the February 14, 2014 IR”. Baxter responded on August 25, 2014 confirming that visual inspection is performed manually at ---(b)(4)----- facility only. Visual inspection at the (b)(4) facility was removed from the BLA in sequence number 0022 submitted 27 June 2014.”

The response is acceptable.

- 8. Please provide a list of tests performed on the Drug Product before and after labeling at your Baxter -----(b)(4)----- facility (----(b)(4)-----).**

Baxter Response:

Testing performed at the Baxter -----(b)(4)----- facility (----(b)(4)-----):

- ID testing of drug product vials and sWFI syringes during receiving and inspection
- 100% visual inspection – semi-automated manual inspection
- AQL testing to ensure that the 100% visual inspection was efficient by Quality function
- 100% vial integrity testing
- 100% barcode scanning of all packaging material (labels, unit cartons)

- AQL-testing to ensure the packaging process was efficient by Quality function: Quality takes Finished Good samples(packages) according to a sampling plan to ensure that all components are packed according to approved bill of material and all lot specific data are printed according to approved bill of material
- Reconciliation of all components after packaging

DMPQ Comment: The above response received on February 28, 2014 did not include the identity test of the final product after labeling. This was discussed during the pre-license inspection of ----(b)(4)----- facility. As a follow up, Baxter submitted additional information on August 25, 2014 which confirmed that the identity test is performed at ---(b)(4)--- before labeling at (b)(4)--. The identity test post labeling is not performed at the same site as that of the release tests. Baxter will perform post labeling identity testing at the (b)(4)- facility, with the same validated assay that is conducted pre-labeling at ---(b)(4)--- and as described in the BLA (3.2.P.5.2 Analytical Procedures ----(b)(4)---). Section 3.2.P.3.3 has been revised to describe when sampling will occur for the post labeling identity testing.

The August 25, 2014 response met the 21CFR 610.14 Identity test requirement and the response is acceptable. (21CFR 610.14 Identity: The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.)

9. **Baxter's request for Categorical Exclusion under 21CFR25.31(j) was not appropriate. OBI-1 is not a biologic product for transfusable human blood or blood component and plasma. Please submit a request for Categorical Exclusion with the basis as outlined in 21CFR Part 25.31(c), and provide your justifications.**

DMPQ Comment: Baxter provided the request for Categorical Exclusion under 21CFR Part 25.31(c). See Environmental Assessment section for details. The response is acceptable.

10. **Please provide a list of FDA licensed products that use the same diluent (Water for Injection) as the one used for OBI-1 from the same manufacturer (-----
------(b)(4)-----) and same manufacturing location. Please provide a tabular comparison of the following: fill volume, fill**

1 Page Determined to be Not Releasable: (b)(4)

(C) Testing performed

Product Specifications and Tests for Release

Test parameter	Specification	Analytical procedure*
Appearance of Solution	----- ------(b)(4)-----	(b)(4)
	----- ------(b)(4)-----	(b)(4)
----- ------(b)(4)-----	----- ------(b)(4)-----	(b)(4)
----- ------(b)(4)-----	---(b)(4)---	(b)(4)
----- ------(b)(4)-----	---(b)(4)---	(b)(4)
	---(b)(4)---	(b)(4)
----- ------(b)(4)-----	---(b)(4)---	(b)(4)
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----- ------(b)(4)-----	---(b)(4)---	(b)(4)
	---(b)(4)---	(b)(4)
----- ------(b)(4)-----	---(b)(4)---	(b)(4)
----- ------(b)(4)-----	---(b)(4)---	(b)(4)
----- ------(b)(4)-----	---(b)(4)-----	(b)(4)
----- ------(b)(4)-----	---(b)(4)-----	----- ------(b)(4)-----
Extractable volume	---(b)(4)-----	----- ------(b)(4)-----
Bacterial endotoxins	---(b)(4)-----	----- ------(b)(4)-----
Sterility	conforms	----- ------(b)(4)-----
----- ------(b)(4)-----.		

DMPO Comment: (b)(4) diluent (sWFI) has been used for two FDA licensed products using the same manufacturing process and the same type of container closure system. In addition, based on information from FACTS, the facility was last inspected by ORA in ----(b)(4)----- and the inspection was classified as NAI. The response is acceptable.

**11. The Letter of Authorization from -----

------(b)(4)----- Systems. Please clarify what (b)(4) Systems are and how they relate to your BLA.**

(b)(4) Response: The -----
----- (b)(4) -----

DMPO Comment: (b)(4) explained the ----(b)(4)-----, so the response is acceptable.

12. The Letter of Authorization from -----(b)(4)----- references DMF “Sterile Water for Injection” but does not have a DMF number associated with it. Please provide a DMF number for the reference. Please clarify how the Sterile Water for Injection from -----(b)(4)----- is related to your BLA.

If the Sterile Water for Injection is used as diluent, please provide the manufacturing location and the FEI. Please provide a list of FDA licensed products that use the same diluent (Water for Injection) as the one used for OBI-1 from the same manufacturer -----(b)(4)----- and same manufacturing location. Please provide a tabular comparison of the following: fill volume, fill equipment, manufacturing process, container closure system used, sterilization process and testing performed.

(b)(4) Response: The DMF number for -----(b)(4)-----.
The sterile Water for Injection (WFI) produced by -----(b)(4)-----.
(b)(4) is used as a diluent to reconstitute OBI-1 [Antihemophilic Factor (Recombinant), Porcine Sequence].

[(b)(4)]

[(b)(4)]

DMPQ Comment: (b)(4) diluent (sWFI) has been used for an FDA licensed product using the same manufacturing process and the same type of container closure system. In addition, based on information from FACTS, the facility was last inspected by ORA in ----(b)(4)----- and the inspection was classified as VAI. The response is acceptable.

March 19, 2014 Information Request

On March 19, 2014, an Information Request from DMPQ was forwarded to Baxter, and a telecon was conducted with Baxter on March 25 to clarify the FDA’s expectations. The response to the information request was received on April 7, 2014. DMPQ questions (in bold) and comments (in bold and italic) and Baxter responses (in plain text) are outlined below.

- 1. Please provide a description of your freeze dryer including manufacturer, model, number of shelves, and trays per shelf, vial capacity, and dimensions or chamber volume. Please describe the minimum and maximum capacity and the typical loading pattern for commercial manufacturing of OBI-1.**

Baxter Response: The technical specifications for the ----(b)(4)----- freeze dryer are presented in **Table 1** below. The lyophilizer loading sequence is from top shelf to bottom shelf.

[(b)(4)]

DMPQ Comment: The response is acceptable.

- 2. In your (b)(4) Freeze Dryer Requalification Report U9BF-RR4(1)-0350, please clarify how the “Freezing Segments” on pages 9 and 11 Section 5.3.1, correspond to the segments in the table on page 7 section 5.3.1 in terms of**

DMPQ Comment: Baxter clarify how the “Freezing Segments” on pages 9 and 11 Section 5.3.1, is correspond to the segments in the table on page 7 section 5.3.1 in terms of temperature and duration and explained the difference between the validation condition (as worst case) compared to commercial production cycle. The response is acceptable.

- 3. Please justify the temperature and duration used for freezing, primary drying and secondary drying. Providing information such as the glass transition temperature, collapse temperature, and/or eutectic temperature may be helpful.

Baxter Response: -----
 -----(b)(4)-----
 -----.

Table 2 outlines the lyophilization cycle and an explanation of the mechanisms taking place. The Process Development for the lyophilization cycle is included in section 3.2.P.2.3 - Changes to (b)(4)- – Lyophilization of Filled Vials and Full Closure Insertion of the OBI-1 BLA.-----
 -----(b)(4)-----

 -----.

[(b)(4)]

[(b)(4)]

DMPQ Comment: Baxter provided the justifications for each step of the freeze drying process. The -----(b)(4)----- . The response is acceptable.

- 4. Please provide more product data using commercial lyophilization cycle. Please ensure you describe your sampling method (e.g. extended sampling, sampling pattern, which shelves sampled and sample locations, number of samples taken at each location), batch size of each run, and testing results (e.g. residual moisture, potency, reconstitution time).**

DMPQ Comment: Baxter provided some testing data related to vial locations in the freezer dryer, but the tests were only for product specific testing such as potency and protein content. No location specific residual moisture and reconstitution time data were provided. Additional data and justifications were provided in response to August 14, 2014 Information Request and the issues were resolved. See August 14, 2014 Information Request Question 2 for details.

- 5. Please confirm that the lyophilization cycle is fixed. Please provide detailed information on any changes made for any of the conformance lot runs.**

Baxter Response: The Lyophilization cycle was fixed at Phase III for development and clinical supply. No changes to the lyophilization cycle were made for the conformance lot runs.

DMPQ Comment: The response is acceptable.

6. For conformance lots, please provide the number of vials went into the freeze dryer and number of vials released for each lot. Please provide visual inspection acceptance criteria and results for these lots.

Baxter Response:

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

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

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

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

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

[(b)(4)]

Baxter also provided detailed visual inspection results for all the lots. The results related to cake appearance are summarized in the reviewer comment below.

DMPQ Comment: The conformance lots produced over (b)(4)-- vials and 100% were visually inspected. Only seven vials had defect related to cake appearance. All seven were marked as "sloping cake". All other defects were related to vials, filling, and sealing process. The response is acceptable.

August 14, 2014 Information Request

On August 14, 2014, an Information Request from DMPQ was forwarded to Baxter, and the response was received on August 25, 2014. DMPQ questions (in bold) and comments (in bold and italic) and Baxter responses (in plain text) are outlined below.

August 14 Information Request, response received on August 25, 2014.

- 1. Please include your assessment of the thermocouples that failed the post validation test to the validation including the locations of these thermocouples.**

DMPQ Comment: Baxter submitted a revised validation report with more detailed location information related to the failed temperature sensors. I reviewed the report and it seems the loss of one sensor per shelf (one out of a total of (b)(4) sensors) was allowed. During the minimum load run, it has (b)(4) shelves, and -----(b)(4)----- shelves had a failed temperature sensor. For the (b)(4) maximum load runs, each of the (b)(4) shelves out of a total of (b)(4) shelves in each run had one failed temperature sensor. So I asked Baxter to justify acceptance of their validations results that included so many failed temperature sensors . See September 8, 2014 Information Request for details. The issue was resolved in the response submitted on September 19, 2014.

- 2. Please provide a summary of the data you have for extended sampling testing (moisture content, reconstitution time etc) in relation to the locations of your lyophilizer (----(b)(4)----- for maximum run and minimum run).**

Baxter Response:

Baxter responded on August 25, 2014 and the information is summarized as following:

Moisture content testing

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

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

[(b)(4)]

Product attributes tests

Baxter included data for the following tests (Study (IG09-2061R))

1. potency by One Stage Coagulation Assay
2. potency by chromogenic assays;
3. -----(b)(4)-----;
4. protein concentration by -----(b)(4)-----.

The sample used are ----(b)(4)----- from the indicated trays and shelves and are representative of the variability across the lyophilizer, consistent with the results of the moisture mapping study (see Figure 4 below). All results of vials

placed in different shelves of the lyophilizer, regardless of the lyo load were consistent and met specifications.

[(b)(4)]

Additional product testing: Experience with commercial process and reconstitution time results

In addition to the development work summarized above, more than (b)(4) lots including (b)(4) development stability, 1 reference, (b)(4) clinical lots, (b)(4) pivotal PV lots and (b)(4) additional PV lots have been produced. All of these lots have been randomly sampled and therefore over time the results obtained are representative

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

DMPQ Comment: *Considering the response provided above and sufficient data provided previously for consistent shelf temperature profile and product temperature mapping, it is acceptable not having the acceptance criteria for secondary drying of the lyophilization cycle validation.*

September 8, 2014 Information Request

On September 8, 2014, an Information Request from DMPQ was forwarded to Baxter, and the response was received on September 19, 2014. DMPQ questions (in bold) and comments (in bold and italic) and Baxter responses (in plain text) are outlined below.

- 1. From your revised validation report U9BF-PQR3(5)-0350 “QB-1 Product Shelf Mapping in the ----(b)(4)---- in the ----(b)(4)----- Facility” submitted August 25, 2014, it seems there was only one sensor for each vial and the loss of one sensor per shelf (one out of a total of (b)(4) sensors) was allowed. If one sensor per shelf fails, the ----(b)(4)----- is no longer maintained. Please justify your acceptance criterion of allowing the loss of one temperature sensor per shelf. In addition, multiple temperature sensors failed during the three validation runs (one minimum load and two maximum loads). During the minimum load run, it has (b)(4) shelves, and each of the (b)(4) shelves had a failed temperature sensor. For the (b)(4) maximum load runs, each of the (b)(4) shelves out of a total of (b)(4) shelves in each run had one failed temperature sensor. Please justify the validity of your validations results with so many failed temperature sensors.**

Baxter Response:

Baxter acknowledges that the justification for the sensor calibration failures was not well detailed in the report. Upon investigation, most of the sensors failed the post-calibration at a higher calibration temperature than what was monitored and reported through the acceptance criteria of the run. The sensors failed the calibration verification at the (b)(4) temperature point following the qualification exercise. All but one sensor (located on -----(b)(4)----- passed the other calibration temperature points, therefore, the data collected was deemed acceptable for data analysis between ---(b)(4)----- . Baxter is submitting the revised (b)(4) Freeze Dryer Performance Qualification Report, which contains justification of the validity of the validation results with failed temperature sensors as requested by the reviewer.

In addition, on September 14, 2014, ---(b)(4)-----, successfully completed a requalification run with a max load in the lyophilizer with the acceptance criteria

that was determined through the above 3 study runs. The study data is currently under evaluation; therefore, no report is available at this time. The sensors were calibrated by a vendor prior to the run. Preliminary assessment of the data at this time look satisfactory, including the sensors in the above location of ----(b)(4)-----, which did not have reportable data in the previous runs. The post run calibration verification has been completed and confirmed as acceptable.

DMPQ Comment: Since most of the pervious deemed failed sensors (except one located on -----(b)(4)----- failed the post-calibration at a higher calibration temperature than what was monitored and reported through the acceptance criteria of the run, and an additional requalification run including the sensors in the above location -----(b)(4)----- was performed with acceptable post run calibration verification, the response is acceptable.