

MEMORANDUM



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

TO: BLA STN 125251/0

FROM: Marion Michaelis, Reviewer, CBER/DMPQ/MRB II, HFM-676
Janie Russell, Biologist, CBER/DMPQ/MRB II, HFM-676

THROUGH: Chiang Syin, Ph.D., Chief, CBER/DMPQ/MRB II, HFM-676

CC: Timothy Lee, Ph.D., Chairperson, OBRR/DH

SUBJECT: **Review Memo** – Octapharma Pharmazeutika Produktionsges.m.b.H.,
license number 1646, BLA for von Willebrand Factor/Coagulation Factor
VIII Complex (Human), for the treatment -----(b)(4)----- of spontaneous
and trauma-induced bleeding episodes in severe von Willebrand disease
(vWD), and in mild and moderate vWD where use of DDAVP treatment is
ineffective or contra-indicated. -----(b)(4)-----

Action Due Date: December 4, 2009

RECOMMENDED ACTION:

Recommend approval of Octapharma Pharmazeutika Produktionsges.m.b.H. BLA for von Willebrand Factor/Coagulation Factor VIII Complex (Human).

SUMMARY:

Octapharma Pharmazeutika Produktionsges.m.b.H. (Octapharma) submitted a BLA for von Willebrand Factor/Coagulation Factor VIII (Human) [Wilate] manufactured at their Vienna, Austria location. Wilate is a human plasma-derived, stable, purified, double virus inactivated concentrate of freeze-dried active human coagulation factor (FVIII) and human von Willebrand Factor (VWF). It is prepared using cryoprecipitate harvested from plasma collected in the U.S. Wilate is supplied as a powder for reconstitution and intravenous injection. The product is labeled to contain per vial 450 IU/900 IU FVIII, and ----(b)(4)---- IU VWF. The product will be reconstituted with the supplied solvent; 5 mL/10mL WFI with 0.1% Polysorbate 80.

Manufacturing includes plasma storage to labeling and packaging of final product. All steps were reported to be using shared equipment and rooms already presented in their Immune Globulin Intravenous (Human), Octagam, submission licensed on 21 May 2004. The firm was most recently licensed for Albumin (Human) on 17 October 2006, which included a pre-license inspection and Wilate is also manufactured in the same area in the Octapharma Pharmazeutika Produktionsges.m.b.H., 235 Oberlaaer Strasse, A-1100 Vienna, Austria, FEI: 3002809097.

However this is the first product that the firm has lyophilized for US licensure. There are three non-US licensed blood coagulation factor products produced in the facility, Factor VIII, Factor IX and PPSB Complex (Octaplex). Also the firm reported that other investigational products of human plasma origin might also be processed in the same areas.

Three (3) pages determined to be non-releasable: (b)(4)

| Filling Size | Filling Volume | Tolerance | Vial Size |
|--------------|----------------|-----------|-----------|
| 450 IU | 5.0 mL | -(b)(4)- | 20 mL |
| 900 IU | 10.0 mL | -(b)(4)- | 20 mL |

Container closure system consists of 20 mL Type -----(b)(4)----- vials, 20 mm Type -(b)(4)--
----- stoppers, and 20 mm ----(b)(4)-- flip off caps. Caps are filled into
----- (b)(4)----- and are sterilized in-house by autoclaving for an SAL of -(b)(4)-.

Vials are supplied by -----(b)(4)-----, international specification number -----(b)(4)----- exists for the vials. Stoppers are supplied in ----(b)(4)---- by -(b)(4)- -----, international specification number ----(b)(4)-----. Caps are supplied by -----(b)(4)-----, international specification number ----(b)(4)-----. Specifications and drawing for the vials, stoppers, and caps were provided. Letters of cross reference were supplied from -----(b)(4)----- for ----(b)(4)---- (record #041, pgs 1-5, and record #710 pgs 1-19 with amendments #2 and #3) and -----(b)(4)----- for --- (b)(4)--- (vol. 3, pgs 257-267 and 290-301; vol. 5, pgs 361-369 and 511-514).

Study report on “Container and Closure Integrity, Wilate”, study number 03P007, was provided. The following were tested after storage at +25°C ± 2°C/----(b)(4)-----, sealed, upright and in the dark:

| Lot No. | Study No. | No. of Samples | Manuf. Date | Batch Size | Start of Study | Incubation Time |
|-------------------|---------------|----------------|-------------|------------|----------------|-----------------|
| ----- (b)(4) ---- | S181020307189 | -(b)(4)- | 05/2003 | -(b)(4)- | 30/07/2003 | ----(b)(4)---- |
| ----- (b)(4) ---- | S182020307189 | -(b)(4)- | 06/2003 | -(b)(4)- | 30/07/2003 | ----(b)(4)---- |
| ----- (b)(4) ---- | S183020312189 | -(b)(4)- | 10/2003 | -(b)(4)- | 17/12/2003 | ----(b)(4)---- |

Three containers from each lot were placed in a -----(b)(4)-----

----- All three batches were tested for sterility including incubation, and passed the container and closure integrity test with no deviations observed. The study report includes references listing the following:

- 000SSR181.03P003.06/International, Final Stability Study Report for Wilate 450 I.U. after 36 months of study 03P003, Change in Lyophilization Stoppers
- 000SSR181.03P007.08/International, Stability Study Report for Wilate 900 I.U. after 24 months of study 03P007, Change in Lyophilization Stoppers

Stoppers:

Lyophilization stoppers (20 mm) are purchased ready to sterilize in -----(b)(4)----- The stoppers are sterilized in-house by autoclaving for a SAL of -(b)(4)-. Flip-Off Caps (20 mm) are also filled into -----(b)(4)----- and sterilized by autoclaving for a -(b)(4)- SAL.

Stoppers are sterilized using one loading pattern in the steam sterilizer -(b)(4)-. The sterilizer is re-validated --- (b)(4) --- by measurement of temperature distribution and inactivation of microbiological challenge standards in the empty chamber and in the loads. -(b)(4)- calibrated temperature probes and -(b)(4)- microbial challenge standards (----- (b)(4) -----) were used for validation with an acceptance criterion of ----- (b)(4) ----- and -(b)(4)- inactivation of ----- (b)(4) -----.

The Pharmaceutical Development Report dated September 2006; states that the --- (b)(4) --- stoppers have been proven to reduce the water uptake during dry-heat treatment to 0.08% (mean value).

Vials:

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

Partially stoppered filled vials are immediately transferred to the freeze drying unit and loaded onto the shelves. Lyophilization occurs under Class -(b)(4)- conditions (unidirectional airflow) over a period of -(b)(4)- the product is frozen at a shelf temperature of -(b)(4)- -----
----- For subsequent drying phases the following parameters apply to achieve residual moisture levels of 0.7-1.6%:

| | | |
|-------------------|----------------------------------------------------------------------------|--------------|
| | 450 Units | 900 Units |
| Time | ---(b)(4)--- | ---(b)(4)--- |
| Pressure | Main drying phase: ----(b)(4)---- - Secondary drying phase: -----(b)(4)--- | |
| Shelf Temperature | ----- (b)(4) ----- | |

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Four (4) pages determined to be non-releasable: (b)(4)

(b)(4)

(b)(4)

Compatibility of Mix2Vial with Wilate, report no. 6MS1031, dated November 2006, was assessed by -----(b)(4)-----

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Validation data for the performance of -(b)(4)- and Mix2Vial was provided (on request) for compatibility with Wilate in documents “Compatibility of the ---(b)(4)-- set with Wilate (6MS1030)” and “Compatibility of the Mix2Vial transfer set with Wilate (6MS1031)” both dated November 2006. These studies demonstrated no occurrence of factor VIII or von Willebrand Factor absorbance to the syringe or infusion set.

Media Fills:

Media fill qualifications are described in section 3.2.A.1.4.5. Aseptic manufacturing process simulations included sterile bulk filtration, sterilization of product/bottles/stopper contact surfaces, aseptic filling, lyophilization and transfer into storage boxes to storage area. Both equipment and personnel are qualified. All personnel must participate in at least one media fill --(b)(4)--. A periodic re-qualification is filled minimally once for each format configuration on a ------(b)(4)-----, and optionally -(b)(4)- ----- for anaerobic organisms, is used as the media. Incubation of media filled units was done for ------(b)(4)-----, than the temperature was raised to -(b)(4)- and incubated for an additional -(b)(4)-. After each incubation period, the containers are visually inspected for the presence of microbial growth. After the first inspection, the containers are stored upside-down during the remainder of the incubation period. Leaking or damaged units are recorded and removed. Any units identified as possibly containing microbial contaminants (cloudy and opaque) are recorded and sent for microbiological identification. After inspection -(b)(4)- filled units are taken as sample for growth promotion testing. The performance qualification must demonstrate a SAL of -(b)(4)- with acceptance criteria of action level contamination rate of -(b)(4)- and a warning level of -(b)(4)- with a 95% CL for -(b)(4)- units in a single run. Any contaminated unit is investigated to identify the route cause and possible origin of the recovered microorganism(s).

[--(b)(4)--]

Requalification of Filling Line -(b)(4)- in January 2006 was performed using three media fills and met the acceptance criteria with a SAL of -(b)(4)-.

The firms SAL is lower than the expected of $\geq 10^{-6}$ for a parenteral product. The action and warning levels also appear to be higher than expected. The firm does not identify what organisms are used for their growth promotion tests of the media. The firm did not identify which lyophilizers were used for their media fill qualification, so it is unknown if both were used and for which batch. The firm also did not identify the number of vials removed for leakage or damage (defect reject rate). The firm provided follow-up information reviewed under section “Amendment 7” and all information provided was acceptable

Conformance Lots Batch Records (BRs):

Conformance lot batch records were included in the submission and upon review the following was found:

- Batch -----(b)(4)----, yield summary records and page 62 comments in Germany require translation.

- Batch ----(b)(4)-----, the beginning information of vWF/FVIII ----(b)(4)----- BR (057HBE18x/02) in German requires translation. Also reasons for samples #13 on page 23.
- All batches for Plasma Cryoprecipitation Separation, page 29 Comments, are in German and require translation.
- All batches for Wilate-vWF/FVIII ----(b)(4)---, code no. 057HBE18x/02, for printouts are in German and require translation.
- Position of trays in freeze dryer not identified in the BR.
- A duplicate copy of Plasma Cryoprecipitation Separation batch -----(b)(4)-----, one for 450 IU and one for 900 IU were present in the BR.

Drying process followed 057SOP123, specifics of drying process are not present in the SOP. Final product label not present in BR and no label reconciliation indicated.

The BRs indicated that the following deviations.

- Batch -----(b)(4)-----, deviation number 06/308, for the “appropriate critical value of the total aerobic microbial count exceeded due to diluting.” The microbial count in room -(b)(4)-, sample ID ----(b)(4)--, was “205 KBE/mL,” the results should be “----(b)(4)----- action limit” and “----(b)(4)----- warning limit.” Cause and effect on product quality are identified as unknown. Immediate action taken was ‘microbe identification; 001SOP203.’ The work step was not identified. QA evaluation of the deviation was “minor” for “microbiological defects in in-process and final control.”
- Batch ----(b)(4)---, deviation number 06/054, -----(b)(4)----- for external cleaning of the plasma cases, work step III.11. Plasma cases are cleaned manually by personnel. The deviation is for plasma cases to be cleaned externally in an automatic facility by a private plasma case washing facility.
------(b)(4)----- The “influence on product quality” was identified as none.
- Batch ----(b)(4)-----, deviation number 06/473, had the appropriate critical value of the total aerobic microbial count exceeded due to diluting. The microbial count (P0) was 1175 KBE/mL, the action limit is ----(b)(4)----- and the warning limit is -----(b)(4)----- Cause and effect on product quality are identified as unknown. Immediate action taken was ‘microbe identification; 001SOP203.’ The work step was not identified. QA evaluation of the deviation was “minor” for “microbiological defects in in-process and final control.” The reason was “P1-microbial count: 52 KBE/mL, P3 – microbial count: 0 KBE/mL, exceedance in PO-microbial count = 1175 = <3-fold action limit.” No species identification was done. Trend information (ADHOC 180, P0/1-Microbial Count, 2006) was included in the submission.

The following were observed in the batch records:

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

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

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

The following was not found in the BR:

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

Follow-up information was provided from the firm to answer all outstanding issues and the information reviewed was found to be acceptable.

Process Validation (PV):

PV summary report (section 3.2.P.3.5) for performance qualification according to the Validation Plan 080MPL06195.100, FVIII/vWF ----- (b)(4)--- and contains the results of the validation beginning with reconstitution of cryoprecipitate until final container. Validation included Method of Preparation 150MOP18x/01/US "Factor VII/vWF ----- (b)(4)---/USA", Method of Manufacturing 150HVO189FFR/04 "Manufacture FVIII/vWF ----- (b)(4)--- Bulk" and 050HVO189AP/01 "Manufacture FVIII/vWF ----- (b)(4)--- Final Product", Final Product Specification 013FPS181/00/US "Wilate 450 or 900 I.U.", and Risk Analysis 150RAN189/01 "FVIII/vWF ----- (b)(4)-----." Critical physical parameters are identified during the process steps and ----- (b)(4)-----

----- Acceptance criteria for the physical parameters were met during PV. Critical parameters were described and are controlled for the S/D treatment. PV acceptance criteria were met throughout the process. Final Container PV report 080RPQ06210.100 according to validation plan 080MPL06195.100 and validation protocol 080RPQ06210.100 were referenced.

Eleven deviations occurred during PV. Four deviations were the result of typing errors or mistakes in documents. The other deviations are as follows:

- There were two deviations on TVC results for sample 0 (----- (b)(4)-----
-----) one for batch ----- (b)(4)--- at 1080 cfu/mL and the other for batch ----- (b)(4)--- at 680 cfu/mL, when the acceptance criteria is ----- (b)(4)---. The investigation included identification of germs, i.e. pathogens. These were considered single events with no impact on product quality, since no further deviations occurred in bioburden or endotoxin downstream.
- One deviation was for an addition to the validation plan for evaluating ----- (b)(4)----- after adjustment.
- ----- (b)(4)-----

----- The deviation resulted in lower process recovery.
- Two deviations for UF/DF step where ----- (b)(4)-----
(deviation number AM 06/433) allowing Factor VIII to migrate into the permeate. This was not considered to have product impact as samples met specifications. This error also caused the ----- (b)(4)- value of the sample ----- (b)(4)--- (for cleaning of the UF/DF after use) of batch ----- (b)(4)--- to exceed the acceptance criterion of ----- (b)(4)---. The initial result of 0.681 mg/mL was confirmed during the OOS investigation at 0.695 mg/mL. Validation was performed on four more batches that all met acceptance criterion.
- A deviation (number AM 06/433) was found based on Method of Manufacturing 050HVO189FFR/04. The result of FVIII in sample ----- (b)(4)-----
----- at 90 IU/mL of batch ----- (b)(4)--- did not meet the acceptance criterion of ----- (b)(4)---. The deviation was investigated. The product was reprocessed by concentrating again by UF/DF with sample ----- (b)(4)- after concentration met the acceptance criterion. ----- (b)(4)-----

----- If sample ----- (b)(4)-

------(b)(4)-----
----- The batch record 054HBE189/08, page 83 of 86, step -(b)(4)-, includes
------(b)(4)-----

----- In the summary review of the FVIII concentration (IU/mL) plotted for each
sample, batch -----(b)(4)----- had a different profile beginning with sample UFR.

- Validation lots:

[
--(b)(4)--
]

Process Validation Final Container Testing:

Process validation included routine testing the final container and one additional test by -(b)(4)-
----- for conformance. The lots met testing criteria, which included sterility, endotoxins and
(residual) water.

In-Process Testing:

One (1) page determined to be non-releasable: (b)(4)

[
--(b)(4)--
]

Final Product Testing: (section 3.2.P.5.1)

Analysis of four consecutive batches for sterility, endotoxin, and water (residual moisture) met specifications, lots: -----(b)(4)---- (450 IU/mL), -----(b)(4)---- (900 IU/mL), -----(b)(4)---- (450

- Residual moisture is tested -----(b)(4)-----

----- The method used is -(b)(4)-
(accuracy ±0.1%) 130SOP130, validation 000VAL130. The specifications are 0.7-1.6%
(sample 16) and -----(b)(4)---- final product.
- ---(b)(4)--- testing is a visual inspection after crimp sealing (for product contamination,
vial defects, and faulty stoppering or flip-off caps) following --(b)(4)--, 130SOP006. The
specification is white or pale yellow powder or friable solid.
- Solubility is testing following -(b)(4)-, 130SOP006. The specification is dissolves in 5.0
or 10.0 mL within -----(b)(4)-----, the reconstituted solution is clear to
slightly opalescent and colorless.
- Sterility testing is by Membrane Filtration, 131SOP120, validation 000VAL106 with a
specification of sterile.
- Endotoxin testing is by -(b)(4)-, 130SOP062, validation 000VAL06, with a specification
of -----(b)(4)---
- Vacuum (in the vials) is testing using a high frequency vacuum tester to confirm the
presence of a vacuum.

Visual inspection occurs in the packaging area. Vials are visually inspected, labeled and packaged into cartons in a continuous line. Residual moisture by ~~(b)(4)~~ is carried out on all vials and those meeting specifications are stored at ~~(b)(4)~~ pending heat treatment. After heat treatment and visual inspection vials are stored at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and protected from light until labeled and packaged.

Packaging includes line clearance prior to initiating packaging operation. Vials are labeled than package into units and transport carts according to written procedures/pack list. All finished goods are stored at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ pending authority release and distribution.

The test method is 131SOP008, “Microbiological Examination of non-sterile products by (b)(4)-
----- according to (b)(4)-----.” Validation code number is 001VAL008 and includes
titles “Examination of Non-sterile Products (Total Viable Count) by (b)(4)----- on
----- (b)(4)-----” (001VAL008 IP 010/01 dated 19 December 2001) and “Examination
of Non-sterile Products (TVC) by (b)(4)----- for Factor VIII (b)(4)-----”
(001VAL008IP180/00 dated November 2000). The SOP and validation reports were provided.
The SOP references (b)(4)--- Microbial Limits Tests. (b)(4)----- is used as the
incubation media. Samples are diluted in (b)(4)-----

------. Calculations take into account any sample dilution.

SOP for “Determination of Water in Lyophilized Products by -----(b)(4)-----”
(130SOP130/000, dated 15 Sept. 2004) was provided. -----(b)(4)-----

---(b)(4)---: Visual inspection:

Sterility Testing and Validation:
Sterility testing uses a membrane filtration method per 001SOP120/01, referencing ---(b)(4)--. Membrane filters with -(b)(4)- pores are used and incubated with Thioglycollate Broth at 30-35 °C and Trypcase Soy Broth at 20-25 °C. Growth promotion tests are done on each media before use. Containers are checked on a regular basis during their 14-day incubation period by visual

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Method validation report, number 001VAL106 FC 18x/01, “Test for sterility by membrane filtration on Factor VIII -----(b)(4)----- was provided. The validation was performed on samples of final container vials from the FVIII --(b)(4)-- batch -----(b)(4)----. This batch was manufactured in 2000 using the current manufacturing procedure. Test strains were added after transferring the contents of the sample container to be tested to the membrane. The media was also inoculated with the test strains before adding to the test container. All containers with bacteria-inoculums were incubated for -----(b)(4)----- and the other containers with yeast and fungi were incubated for -----(b)(4)-----. Growth of the test strain was visually comparable to the positive control. The SOP and the validation met the requirements per ---(b)(4)---.

Endotoxin Testing and Validation:

(b)(4)

[Redacted text block containing multiple paragraphs of information, all obscured by black boxes.]

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

Material Flow:

Material flow is described in section 3.2.A.1.1.3. The firm provided detailed material flow floor plans, C/PR1/005 – “Production 1 -(b)(4)- Chart Flow Chemicals”, CF/PR1/004 – “Production 1 ----- (b)(4) ----- (Fine Fractionation) Chart Flow Chemicals”, and DF/PR1/006 – “Production 1 ----- (b)(4) ----- (Aseptic Production) Chart Flow Chemicals & Primary Packaging Materials”. Materials are separated for production and aseptic processing steps. -(b)(4)- vials are washed, dried and depyrogenated by sterilizing in a ----- (b)(4) ----- before being automatically transported into the filling room -(b)(4)-. Stoppers are washed, --(b)(4)-- and sterilized by autoclaving; then transferred via sterile passage into filling room -(b)(4)-. Material flow appears adequate for the facility.

Personnel Flow:

Personnel flow is described in section 3.2.A.1.1.4. Entrance to the facility is made through personnel locks and require code cards for access. The firm provided detailed personnel flow floor plans, CF/PR1/002-1 – “Production 1 Chart Flow Personnel, Pt. 1” [Basement], and CF/PR1/002-2 – “Production 1 Chart Flow Personnel, Pt. 2” [-(b)(4)- Fractionation, -(b)(4)- Fractionation, Aseptic Manufacturing]. Gowning is different for each production area and room classification. The gowning uses different colors to identify personnel working in the different production areas. Personnel flow and gowning appears adequate for the facility.

Waste Flow:

Waste flow is described in section 3.2.A.1.1.5. The firm provided detailed waste flow floor plan, CF/PR1/016-1 – “Production 1 Chart Flow Waste.” Production waste leaves the facility through either the refuse lock or the material lock. Waste flow appears adequate for the facility.

CIP and SIP:

The firm has -(b)(4)- CIP and CIP/SIP systems (----- (b)(4) -----) for cleaning and sanitization of equipment in place. The CIP process is controlled for temperature ----- (b)(4) ----- of agents by ----- (b)(4) ---. For SIP, --(b)(4)-- is also controlled with the same parameters as for CIP. Cleaned equipment in the aseptic processing area are sanitized or sterilized by clean steam (autoclave) or dry heat. ----- (b)(4) ----- used for product transfers are sanitized prior to use and disposed of after use. Clean steam generated meets the same specifications as -(b)(4)- WFI. During PQ, clean steam from -(b)(4)- samples met all required specifications. The firm has CIP process procedures/sequences for fractionation and pre VI, and post VI and aseptic manufacturing areas. Per batch records (BRs) for plasma cryoprecipitate separation the standing times for tanks after cleaning if -(b)(4)- a CIP run must be performed, for separator parts if -(b)(4)- complete cleaning must be performed and for -(b)(4)- filters after sanitation if -(b)(4)- a renewed sanitation must be performed. Per BRs for bulk the standing times of the containers to be CIPed was ----- (b)(4) -----. An overkill approach is used for sterilization/sanitization process with acceptance criteria as:

The firm has established validated cleaning procedures for a multiple product facility. The firm has validated cleaning procedures for -----(b)(4)-----

[illegible]

As production advances through the process, the process material moves from Class ---(b)(4)--- through to Class -(b)(4)- and --(b)(4)-- to Class --(b)(4)--- for sterile filtration and Class -(b)(4)- for filling. Cleaning and sanitization/sterilization procedures are validated and routinely monitored. Room cleaning is done after each batch prior to the next batch entering the room for processing. The firm has a defined schedule for cleaning each production room. The schedule for clean rooms Class ----(b)(4)----- was included. Spills and contamination are removed immediately. Cleaning and disinfection agents are used per written procedures, rotated, and effectiveness demonstrated in validation studies.

Intervals of the environmental monitoring are defined based on the activity and proximity to the product and the quality of the air. Parameters monitored include -----(b)(4)-----

monitoring during manufacturing of each batch for Class -(b)(4)-. Gowning is only monitored in Class -(b)(4)- during manufacture of each batch. Other manufacturing areas (Class ----(b)(4)----) are monitored on a less frequent basis for microbial and/or particle counts. -----(b)(4)----- are also used as a confirmatory check of surfaces, walls, equipment, personnel gowning and hands. Warning Limits (alert, WL) and Action Limits (AL) for -----(b)(4)-----

[
--(b)(4)--
]

[
--(b)(4)--
]

When a microbiological action limit is exceeded, the organism is identified by genus and species where possible. The identification is used in determining the source of the contamination. Microbial trending is performed by room, operator, and surface locations to assist in investigations. A review of all environmental data is performed ----(b)(4)--- for results and trends, investigations of excursions and evaluations, and effectiveness of initiated CAPAs. Monitoring is part of the batch records and reviewed for the final release of the product. Actions taken when specified limits are exceeded were included in the submission. Any affected product is quarantined until the contamination source is identified and a risk for the quality and safety of the product can be excluded.

HVAC:

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

[
--(b)(4)--
]

One (1) page determined to be non-releasable: (b)(4)

[
--(b)(4)--
]

Water Systems:

There are three systems for water purification, deionized water, purified water and WFI. The systems are used for the following:

- 1. Deionized water
 - -----(b)(4)-----
 - -----(b)(4)-----
- 2. Purified water ----(b)(4)----- -

- 3. WFI
 - -----(b)(4)-----
 - -----(b)(4)-----
 - -----(b)(4)-----

The specifications for Deionized Water are:

[
--(b)(4)--
]

The specifications for Purified Water, USP, are:

[
--(b)(4)--
]

The specifications for WFI are:

[
--(b)(4)--
]

The systems consist of the following in order:

1. Deionized (DI) water, capacity of -(b)(4)-, is operated at ambient temperatures. The system consists of -----(b)(4)-----
-----.
2. Purified water (PW), capacity of -----(b)(4)----- The distribution system consists of -----(b)(4)-----

----- No changes have been made to the system since initial validation.
3. Water For Injection (WFI)
 - -----(b)(4)-----

 - One WFI holding tank, -----(b)(4)----- capacity with level and temperature control, -(b)(4)-) with -(b)(4)- vent filter which is integrity tested -----(b)(4)-----

-----.

- Distribution system, WFI is circulated at (b)(4). Temperature excursions are allowed for a maximum of (b)(4).
 - A summary of the WFI IQ and OQ included acceptance criteria and results that the system met all criteria.
 - (b)(4)
 - (b)(4)
 - (b)(4)

• (b)(4)

• (b)(4)

The monitoring specifications and frequency for monitoring all water types was included in the submission. The firm has a written routine monitoring program that defines the actions to be taken when limits are exceeded. The submission notes that a review of all monitoring data is performed monthly by QA to evaluate results; review investigations of excursions and evaluations; and follow-up of effectiveness of initiated CAPAs.

Computerized Systems:

Several manufacturing steps for WILATE are supported by computerized systems. There is a low degree of automation for production with no automated decision-making systems in batch processing. Automation includes remote control systems (RCS), sequence control systems (SCS), and package unit systems (PU). Validation is based on Good Automated Manufacturing Practice guidelines (GAMP) which includes responsibilities, system life cycle, validation procedure and required documents as described in the Validation Master Plan and SOPs. GAMP Software categories are (1) operating systems, (2) standard instruments, (3) standard “off the shelf” software packages, (4) configurable software packages, and (5) bespoke systems. Computerized systems are classified according to parameters defined in GAMP for validation.

The firm uses the following computerized equipment:

- -----(b)(4)----- for the fractionation area used in manufacturing step -(b)(4)-. Computer controlled for temperature and stirring. PQ included temperature mapping studies using simulated process conditions. PQ parameters included -----(b)(4)-----

. All tests met the acceptance criteria.
- -----(b)(4)----- for buffer preparation used in manufacturing step -(b)(4)-. Computer controlled for temperature and stirring. PQ included -----(b)(4)-----

. All tests met the acceptance criteria that temperatures were reached and kept constant.
- CIP/SIP Station (- (b)(4) -) used for -----(b)(4)----- tanks in the --(b)(4)-- fractionation area. System includes temperature controller and -----(b)(4)---- measurement. All automated functions of the CIP/SIP system were demonstrated to work within specification. Cleaning validation results proved the effectiveness and reproducibility of the CIP/SIP process of the chosen parameters.
- CIP/SIP Station (- (b)(4) -) used for -----(b)(4)----- tanks in the --(b)(4)-- and aseptic manufacturing area. System includes temperature controller and -----(b)(4)---- measurement. All automated functions of the CIP/SIP system were demonstrated to work within specification. Cleaning validation studies were performed on the --(b)(4)-- system and met acceptance criteria.

- Filling Machine, Line ----(b)(4)---, PQ included ----(b)(4)--- media fills with filling volume verified by calibrated -----(b)(4)-----

- Bottle Washing and Depyrogenation Tunnel (----- (b)(4) -----) includes controls for temperature and pressure. The depyrogenation cycle is --- (b)(4) --- re-qualified in addition to the ----(b)(4)---- media fills. No deviations have been reported for malfunctions of the control system of the washer or tunnel.

IT systems are utilized for the control and tracking of plasma donations including material identification and labeling, stock administration and warehouse management of plasma, auxiliary material, primary and secondary packaging, intermediates and final products, tracking of material flow within facility, and product history from distributed final product to plasma donations which is supported by the ----- (b)(4) ----- . The ----(b)(4)---- system is based on an -(b)(4)- database. A redundant ----(b)(4)---- advanced server hosts the system with workstations equipped with barcode scanners and label printers. The final validation report for the --(b)(4)-- system approved 30 June 2003 was provided with qualification for extension of functions and software updates with deviations summarized. There were no open deviations remaining after validation. All system changes and revalidations are documented in a log book. Revalidation was stated to include a review of the system and all documentation for 2 years.

A Laboratory Information and Management System (LIMS) is used for support of batch release; collection, evaluation and reporting of analytical data (except incoming control); archiving of QC data; support for environmental monitoring/stability studies; generation of documents; automatization of laboratory workflows; and information management. The LIMS is an -(b)(4)- database and all applications were reported as being validated. The final validation report for the LIMS system approved 19 July 2006 was provided with qualification and deviations summarized.

Solvent Manufactured by Octapharma:

The manufacturer is Octapharma -(b)(4)- located at ----- (b)(4) ----- . The solvent is 0.1% Polysorbate 80 in WFI as quantities of 5 mL and 10 mL per vial. The vials are 10 mL type -(b)(4)- USP quality from ----- (b)(4) ----- and are closed with -(b)(4)- grey ----- (b)(4) ----- stoppers of -----(b)(4)---- quality from ----- (b)(4) ----- . The packaging components are latex free. The Caps are ----- (b)(4) ----- flip off seals in the color blue from ----- (b)(4) ----- . The manufacturing process comprises of simple mixing of the excipients and filling of the mixture under aseptic conditions. The Polysorbate 80 is not thermo-stable, the solution is sterile filtered into pre-sterilized containers and closed with sterilized stoppers.

The manufacturing formula for a batch is ----- (b)(4) ----- , which are ----- (b)(4) ----- respectively. Weighing and dissolution of the components is performed under Class -(b)(4)- environment in a -(b)(4)- tank to final concentration. Sampling (sample -(b)(4)- with limit of -(b)(4)-) for Total Viable Counts (TVC) is done immediately prior to ----- (b)(4) ----- through a ----- (b)(4) ----- tank, located in Class -(b)(4)- environment. The filter is integrity tested before and after filtration. The bulk solution can than be stored for ----- (b)(4) ----- .

The filling of the solvent is performed under aseptic conditions in a Class -(b)(4)- environment. Immediately before filling, the solution is ----- (b)(4) -----

----- (b)(4) ----- with a nominal pore size of (b)(4)-. Sampling (sample (b)(4)- with limit of (b)(4)---) for TVC is done ----- (b)(4) ----- . The filter is integrity tested before and after filtration. The solution is filled into ----- (b)(4) ----- vials. The filled vials are sealed with stoppers and capped under Class (b)(4)- before being transferred through a mouse hole of the barrier housing to be conveyed to the crimping machine. The closed and sealed vials move continuously from the filling line to an ink-jet unit where each vial is marked with a unique batch number on the cap before the vials are packed for intermediate storage. Samples are transferred to QC for testing. The filled vials are 100% visually inspected for fill volume, visual particulate matter and control of cap, stopper and vial defect, and the ink-jet mark. Rejected vials are discarded. The accepted final containers are stacked into storage containers, which are closed, sealed and labeled with the product name, fill size and batch number before being transported back into the storage area and stored at (b)(4)- pending QC release.

Results of in-process controls for three consecutive batches of 5 mL or 10 mL batches produced in 2006 are:

[(b)(4)]

The TVC test method is entitled the “Microbiological Examination of non-sterile products by (b)(4)--- Method according to (b)(4)---” under 131SOP008 with the validation under OC06-O108 entitled the “Applied Validation of Microbial count, (b)(4)-----.” The method references (b)(4)--- Microbial Limits Tests for quantitative evaluation of aerobic mesophilic bacteria and fungi.

Validation (OC06-0108) with the solvent was performed using three consequent production batches ((b)(4)-----) before sterile filtration. The results were determined to be acceptable.

Process validation (report OC06-0106) for maintenance of sterile conditions during production was performed for three consecutive batches of each filling size (5 and 10 mL) in August 2006. All in-process controls were within limits and the product complied with final product specifications.

Filling was performed with a sterile filter assembled just before the filling needles. Samples were taken of the bulk (b)(4)----- for homogeneity. Samples were taken during filling from (b)(4)----- for homogeneity. Homogeneity limits are (b)(4)----- w/w for the Polysorbate 80 concentration. All holding times were before sterile filtration for more than (b)(4)----- . For the storage of the sterile filter solution at (b)(4)-, media fills (performed (b)(4)-----) include the storage of broth for at least (b)(4)- prior to filling with a trend of (b)(4)----- per batch in Feb 2003, Sept 2003, and March 2004 for (b)(4)--- each, and in March 2005 for (b)(4)---. Filling weights were done on every vial of all batches and were within the criteria. The specifications for the final product are:

- Visual inspection is done per 130SOP006/01 using a screen with a black and white background. The (b)(4)- test for endotoxins (130SOP062/00) uses the (b)(4)---
----- . This is the same procedure used for the Wilate product. The report (000VAL062 WE Solvent /00) entitled “Determination of Bacterial Endotoxin in SOLVENT (0.1% Polysorbate 80 in (b)(4)-----

Using a -----(b)(4)----- Assay Acc. ----(b)(4)----” was provided. The testing was done in accordance with SOP 130SOP062/00. Samples were taken of three batches; ---(b)(4)--- (filling size: -(b)(4)-), ----(b)(4)---- (filling size: -(b)(4)-), and ---(b)(4)--- (filling size: -(b)(4)-). Undiluted samples and sample dilutions of 1:2 and higher gave satisfactory sample response characteristics for all lots. The assay was reported to meet acceptance criteria for the evaluated parameters.

Sterility testing uses a membrane filtration method per 001SOP120/01, referencing ---(b)(4)---, as is done with the Wilate product. Membrane filters with -(b)(4)-- pores are used and incubated with Thioglycollate Broth at 30-35 °C and Trypcase Soy Broth at 20-25 °C. Growth promotion tests are done on each media before use. Containers are checked on a regular basis during their 14-day incubation period by visual inspection for turbidity. If a turbid container is detected, the effective deviation management system is followed.

Method validation report, number OC06-0109, entitled “Validation of Sterility test for Aqueous 0.1% (w/w) Polysorbate 80 Solution, sterile. Method S026” was provided. The validation was performed on samples of three production batches: -----(b)(4)-----
----- Validation was done using -----(b)(4)-----
----- One vial of each product was for each microorganism was infected by -----(b)(4)----- All containers were incubated for 14 days at 20-25 °C for Tryptic soy broth (TSB) and 30-35 °C for Fluid Thioglycollate medium. Growth was found after 2 days in anaerobic median inoculated wit *C. sporogenes*, *P. aerugionosa* and *S. aureus*. After 2 days growth was also found in both media inoculated with *C. albicans* and *B. subtilis*. In aerobic medium inoculated with *A. niger* growth was found after 3 days. The negative control remained negative for the entire 14 days. The validation showed that method S026 (Sterility testing of drugs by membrane filtration) can be used for sterility testing of the solvent.

Container closure (packaging) integrity was provided in report OC-06-0103 entitled “Microbiological Challenge Test for Container/Closure Integrity of Vial -(b)(4)-, Stopper -(b)(4)- and Cap -(b)(4)- Initial Test” dated August 29, 2006. The primary package integrity was performed on 20 mL vials, rubber stopper and cap. The vial neck of the 20 mL vials is identical to the vial neck of the 10 mL vials, and the stopper and cap are the same, therefore the firm concluded that the test is valid for both vial sizes. -----(b)(4)-----

Manufacturing and filling occurs on the (b)(4)- floor in Building (b)(4)- with storage of filled vials on the (b)(4)- floor; and inspection and packaging occur in Building (b)(4)-, room (b)(4)- -----. Filtration is one in rooms -----(b)(4)------. Filling is in room (b)(4)-, crimping in room (b)(4)- and ink-jet in room (b)(4)-. Building ---(b)(4)--- also are used for main storage

for raw materials and products. Other products manufactured in the same area include Octonativ-M (monoclonal purified factor VIII concentrate), Octanate (purified factor VIII concentrate), Nanotiv (highly purity factor IX concentrate), Albumin/Albuminativ (human serum albumin 4% and 20%), Atenativ (high purity antithrombin III concentrate), Gammanorm (immunoglobulin for intramuscular or subcutaneous use), Octagam (immunoglobulin for intravenous use, FDA licensed), Rhesonativ (immunoglobulin anti-D), sterile WFI diluent, and -----(b)(4)-----).

Access to the production areas are controlled and restricted to authorized personnel by use of code cards with electronic reading devices with separate gowning facilities for entry.

Equipment used for manufacturing maybe used for other products. Shared equipment is either cleaned by validated automated or manual procedures, or a combination of both. Automated CIP cleaning is used to clean stainless steel tanks using potable water followed by -----(b)(4)-----
----. Manual cleaning uses ----(b)(4)----- washing detergent with -----(b)(4)-----
----- cleaning is also used for small parts. Any equipment with product contact surfaces in the aseptic operation area undergoes final sterilization by autoclaving, -----(b)(4)-----, using clean steam. Major process equipment was identified in the submission.

Contamination and cross-contamination are prevented using procedures for segregation and containment by areas, manufacturing operations, equipment, personnel, raw materials, environmental air, and water quality.

Environmental monitoring and HVAC controls were included in the submission, reviewed and found to be acceptable.

Contamination from other products is minimized by processing of one product per room, validated cleaning of multi-use equipment, routine environmental monitoring, routine monitoring of water and steam quality, personnel flow to restrict access to clean areas only to authorized and trained production staff, and use of media fills to confirm aseptic process validation. Equipment and room contamination is minimized by processing only one batch at a time, clearly marked status of equipment (i.e. clean, dirty, in use, production step), use of closed systems, validated equipment sterilization, and clearance of the room or processing area (i.e. all product, samples, non-used chemicals, non-used materials, mobile equipment, cleaning and sanitization of fixed equipment, removal of wasted, and cleaning of room). Personnel contamination control measures include restricted access, dedicated gowning, training, and personnel flow.

Media fills for the aseptic filling process are performed on a ---(b)(4)--- basis with -(b)(4)- with filling done at the normal speed for the vial size. For on-going re-qualification bracketing is used for the process simulation.

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

The firm provided product, material and personnel and waste flow diagrams in the submission.

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

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

The environmental monitoring program was included in the submission with an explanation on the frequency of monitoring.

Particle counts are performed using an ----- (b)(4) ----- selected sites in the production areas. In the filtration room - (b)(4) - and in filling room - (b)(4) - particle counts are performed by ----- (b)(4) ----- . Microbial control is performed by both - (b)(4) - ----- are used as a confirmatory check of surfaces, walls, equipment, personnel gowning, and hands.

Alert limits were set based on historical data and the action limit. The limits are evaluated - (b)(4) -. Room Classes - (b)(4) - areas are released - (b)(4) - based on the results from samples tested. The data for basic and batch-wise monitoring for the different rooms are assessed. Release of product is not done until the relevant production areas are released. Trending and assessment of data in Class - (b)(4) - areas is done - (b)(4) -. Long-term trending of the environmental and personnel monitoring data is made - (b)(4) - for Classes - (b)(4) - with a comparison of the previous - (b)(4) -. The - (b)(4) - environmental monitoring report is reviewed to evaluate the efficacy of the monitoring program and determine if the frequency of the monitoring or the alert limits need to be changed.

The water systems include potable water used to supply the purified water (PW) (RO/EDI), which is used to feed water for WFI and for laboratory use. The ----- (b)(4) -----

----- . Each system is validated to a specified program design that is appropriate to the water quality requirements. Each system is routinely monitored for water quality. The PW meets - (b)(4) - requirements. For the WFI system, coolers are installed at the point of use to provide cold or room temperature WFI. The requirements and monitoring for WFI were included in the submission, reviewed and found to be acceptable.

Computer systems are identified as administrative IT systems, large control systems (LCS), small control systems (SCS), programmable logic controllers (PLC) and applications. In general the manufacturing process is manually monitored with certain manufacturing steps supported by computerized systems. There are no automated decision-making systems for batch processing. There is no LCS for the solvent manufacturing process. SCS are based on PLC with a PC interface that allows a sequence of functional steps, where the operator initiates the sequence. Examples of SCS are autoclaves and label printers. PLC controlled equipment include the - (b)(4) - depyrogenation tunnel and the ---- (b)(4) ---- filling machine which are supported by automated monitoring. For PLCs, LCS, and CSC; the operational qualification of the computerized functions are performed together with the mechanical part. Validation consists of IQ and OQ. Other automated equipment includes - (b)(4) - vial washer, dish washers, crimping machine, marking, and visual inspection machines. Changes to computer systems require an impact assessment before implementation, and authorization from QA and the system owner.

The vial washer monitors physical parameters including pressure (cleaning air), temperature (WFI, ----- (b)(4) -----), and time (duration of cleaning). The depyrogenation tunnel

Solvent Manufactured by -(b)(4)-:

The manufacturing formula for a batch is -----(b)(4)-----
----- . Weighing and dissolution of the components is performed in a
-----(b)(4)--- tank under class -(b)(4)- environment. Sampling (sample -(b)(4)- with limit of
-----(b)(4)----) for Total Viable Counts (TVC) is done prior to -----(b)(4)----. The filter integrity
tested -----(b)(4)-----.

(b)(4)

[
]

[-(b)(4)-]

The TVC test method is entitled the “Microbiological Examination of non-sterile products by -----(b)(4)----- according to ----(b)(4)----” under 131SOP008 with the validation under VBM-35688_01 entitled the “Validation of Bioburden Determination in Solvent 0.1%.” The method is the same as for the Solvent Manufactured by Octapharma.

Validation report (VBM-35688_01) with the solvent was performed however did not identify what batches were used. Organisms uses in the validation were -----(b)(4)-----

----- The recovery of microbial count was $\geq 70\%$ after filtration of product in comparison to the positive controls. The negative controls did not show growth. The results were reported to have met the acceptance criteria.

Process validation report (100VAR902_5/00 for 5 mL and 100VAR902_10/00 for 10 mL) for maintenance of sterile conditions during production was performed for three consecutive batches. All raw materials met specifications, all in-process controls were within limits and the product complied with final product specifications for both fill sizes. -----(b)(4)---- batches were produced for validation 100VAR902_5/00 and 100VAR902_10/00 respectively, however only partial quantities were filled with the remaining solution discarded. The standard batch formula is -----(b)(4)-----.

The -----(b)(4)----- were determined for samples taken from the -----(b)(4)----- of filling. All measured parameters were within specification limits. Environmental monitoring was performed during the filling with the results within the required alarm limits. All vials were inspected for filled height, undissolved particles and general appearance using a semi-automatic inspection machine with segregation of vials that did not conform within the tolerance of -(b)(4)- for good vials. The results for the final product were included in the submission, reviewed and found to meet acceptance criteria.

Visual inspections (130SOP006), -(b)(4)- test for endotoxins (130SOP062), and the sterility test method (131SOP120/01) are the same method as for the Solvent Manufactured by Octapharma. The -(b)(4)- validation report (000VAL062 WE Solvent /00) was also the same. -(b)(4)- also has an endotoxin method (130SOP108/00) entitled “Determination of Bacterial Endotoxins by -----(b)(4)----- acc. -----(b)(4)----” for monitoring of process water. This method uses -----(b)(4)----- as well. The validation report (000VAL108 WE Solvent /00) entitled “Determination of Bacterial Endotoxin in SOLVENT with -----(b)(4)----- Using -----(b)(4)-----” was provided. Samples were taken of three batches; -(b)(4)- (filling size: 10 mL), -(b)(4)- (filling size: 10 mL), and -(b)(4)- (filling size: 5 mL). The assay was reported to meet acceptance criteria.

Method validation report, number 001VAL106 SOLVENT/00, entitled “Test for Sterility by Membrane Filtration on SOLVENT -----(b)(4)-----” was provided. The filters were treated with the solvent (-(b)(4)- final containers per strain) than each microorganism at 10-100 CFU was filtered. -----(b)(4)-----

----- After the -(b)(4)- incubation all (product and positive control) had intense growth demonstrating that the solvent had no bacteriostatic or fungistatic activity.

Container closure (packaging) integrity was provided in report 000SSRCCITSOLV.00/INT entitled “Study Report on Container and Closure Integrity, Solvent, Study No. CCITSOLV.”

The study was carried out on product that had been stored at +2 to +8 C before the study was started in September 2006 within the established shelf life of the product. The lots were

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

----- All results were met the acceptance criteria for sterility.

Manufacturing occurs on the - (b)(4) - floor of the production building. Major process equipment

was identified as ----- (b)(4) -----

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

Media fills for aseptic filling and stoppering operations are validated using process simulations

with a microbiological medium (----- (b)(4) -----) in place of the product. The

process simulations include all of the process steps of a typical aseptic filling (i.e. equipment

assembly, dosage pump calibration, in-process controls, monitoring activity interventions, etc.).

Worst-case interventions (i.e. ----- (b)(4) -----

-----) are also included in the media fill protocols. Interventions are carried out

under the observation of a supervisor in the filling suite. For initial qualification, - (b)(4) -

consecutive successful media fills were required. For requalification, ---- (b)(4) ---- successful

process simulations are required. The requalification addresses the various factors associated

with a worst-case scenario, including the maximum number of shift changes and the maximum

filling time. The filled vials are inspected and incubated for ----- (b)(4) -----

-----, and examined for microbial contamination. Positive controls are run on samples from the

----- (b)(4) ----- by inoculating the vials after the initial incubation with

microorganisms to show will support growth. These microorganisms are ----- (b)(4) -----

----- The worst case approach is used to select the media fill parameters,

which are selected using bracketing. These include the ----- (b)(4) -----

----- (b)(4) ----- . Two vials were selected to represent the worst cases. The two vials are - (b)(4)- vials (----- (b)(4) -----) and ---- (b)(4) ---- vials ---- (b)(4) ----- .

However - (b)(4)- vials were chosen over the ----- (b)(4) ----- vials due to the amount of media required and space for incubation. The - (b)(4)- 5 mL vials have the same neck diameter as the - (b)(4)- 100 mL vials and are filled at the lowest speed in order to provide the same product exposure time. Stoppers were also considered and selected from the worst case conditions that have the highest probability of popping off the vials during the stoppering operation. Each operator in the filling suite must participate in a media fill - (b)(4)- and is requalified by filling ---- (b)(4) ----- . The specifications for media fills were included in the submission. Also included were results of six recent ---- (b)(4) ---- media fills. There were no contaminated units.

In the event of a media fill failure, an investigation is performed by production, QC and QA personnel. The investigation includes isolation and speciation of the organism; evaluation of microbiological monitoring; review of equipment sterilization records; HVAC system testing; review of clean room differential pressures, air velocities, etc.; production operator behavior and training; batch record review; interviews with personnel; review of historical media fill reports; and QA reports. Production is suspended or fills quarantined until the investigation is completed and - (b)(4)- consecutive media fills are successful. The product previously made before the last successful media fill and the failure will be evaluated for impact.

The firm provided product, personnel, and material flow diagrams in the submission.

The ventilation system is designed so that different production facilities are equipped with dedicated Air Handling Systems (AHS). ----- (b)(4) -----

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

Microbiological monitoring of the environment is performed. Clean room monitoring includes ----- (b)(4) ----- . Personnel working in the filling room are monitored by ----- (b)(4) ----- .

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

Environmental monitoring information was included in the submission. The alert and action limits for the Sterile Production C (SPC) area were also included. The firm has procedures for dealing with environmental monitoring deviations which includes an evaluation for the identification of the organism, risk to product and trending data; and measures that may be taken such as cleaning, training, and additional testing of products.

WFI quality clean steam is produced by a pure clean steam generator (b)(4). The clean steam is used for equipment sterilization (autoclaves and SIP stations) and terminal product sterilization in autoclaves. The clean steam is monitored for its microbial and chemical quality. Condensate is monitored (b)(4) for endotoxins and TVAC using the same methods as for WFI. If alert or action limits are exceeded the same actions occur as with WFI.

Review of Amendment #7:

1. During Process Validation there were two deviations reported on Total Viable Count results for sample -----(b)(4)-----) one for batch ----(b)(4)---- at 1080 cfu/mL and the other for batch ----(b)(4)---- at 680 cfu/mL, when the acceptance criteria is ----(b)(4)----. These were considered single events with no impact on product quality. Provide justification of this determination including root cause and corrective actions taken.

35/42

2. *In-process endotoxin specifications are listed as “For Information Only.” Please provide justification for not setting in-processing limits for endotoxin and submit actual data for each in-process step where endotoxin was tested.*

Endotoxin is not performed routinely for other currently approved markets, however was introduced for the conformance lots manufactured for the USA. The firm has committed to implement endotoxin routine testing for sample -(b)(4)- at a limit of -(b)(4)- and sample -(b)(4)- for a limit of ---(b)(4)--. The limit for sample -(b)(4)- corresponds to the limit in the final product specifications. Results from in-process testing on samples -(b)(4)- were < 0.15 IU/mL and <0.16 IU/mL on -(b)(4)- batches.

3. *Provide validation summary data for hold time after Clean in Place and Steam in Place before use.*

Holding times of cleaned equipment were evaluated after CIP by investigating the microbial load on the equipment surfaces (product contact positions such as inside walls, area around bottom valves and necks) immediately after the pre-defined maximum allowable storage period before use. These evaluations were completed in October 2004 for all equipment used in the Fractionation and Purification --(b)(4)-- area. After CIP, equipment is kept for up to -(b)(4)- for Fractionation and -(b)(4)- for Purification areas. In the Fractionation and --(b)(4)-- area tanks are only CIP, where in the Purification --(b)(4)-- area tanks are CIP and SIP. The results were included in the information provided and found to be acceptable.

4. *Identify the batches that the optional -(b)(4)- steps of the unsterile bulk solution (after step -(b)(4)-) were performed. In addition, please provide the results of the in-process and final product testing before and after the -(b)(4)-.*

During the production of the conformance batches, no batch exceeded the maximum factor VIII concentration of -(b)(4)- in sample -(b)(4)-, therefore none were -(b)(4)-. However there were two batches produced for the European market in 2005 where -(b)(4)- was performed. Results of these batches were provided in the amendment

5. *Study report on “Container and Closure Integrity, Wilate”, study number 03P007, stated there was a change in lyophilization stoppers with reference to 000SSR181.03P003.06/ International, Final Stability Study Report for Wilate 450 I.U. after 36 months of study 03P003, and 000SSR181.03P007.08/ International, Stability Study Report for Wilate 900 I.U. after 24 months of study 03P007. It is not clear the stoppers listed in the BLA were the same as the ones used for “Container and Closure Integrity” and lyophilization studies. Please clarify.*

The firm reported that the stoppers used in the study reports “Container and Closure Integrity Testing Study” no. 000SSRCCIT.03P007.00/INT and the European Stability Studies with the freeze-dried product no. 000SSR181.03P003.06/International and 000SSR181.03P007.09 /International are the same as listed in the BLA.

6. *Please provide a summary of media fill report and the results from the most recent media fill. In the summary report, please identify the microorganisms used for growth promotion tests of the media, the lyophilizers used, and the number of vials removed for leakage or damage (defect reject rate) during media fills.*

The media fill report for the first half-year 2007 was provided. The media fills met the acceptance criteria.

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

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

Simulation of the storage time (----- (b)(4) -----) for bulk, the sterile filtered growth medium solution was stored for a certain time period at room temperature before filling with acceptable results for storage at ----- (b)(4) -----.

Operators were randomly assessed and qualified during the media fills. Two technicians had OOS results before filling, one from fingerprints and one overall. Additional hygiene training was initialized with the focus on the sampling techniques and clothing in the clean room. Results of the media fills remained satisfactory.

Historical media fill results after modifications in the summer of 2005 were also include in the amendment.

There are - (b)(4) - identical lyophilizers used in the manufacture of freeze dried products. These are identified as ----- (b)(4) ----- which were both used in the most recent media fills with batches ----- (b)(4) ----- respectively.

The number of vials removed for leakage or damage (defect reject rate) during visual inspection was recorded in the report and in respective batch records for the filling. For the two most recent media fills, these were both 0 containers removed.

7. *For lyophilization:*

- a. *Please provide validation data with actual measurements and acceptance criteria for temperature distribution of shelves including temperature changes (ramps) during OQ.*

Temperature distribution of shelves is measured every --(b)(4)-- for re-validation of the lyophilizers.

[
--(b)(4)--
]

- b. *Please provide summary measurements with acceptance criteria for cooling speed, heat-up speed, and evacuation time/rate from IQ/OQ.*

[
--(b)(4)--
]

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

- c. *Please provide sterilization validation report including temperature distribution within the chamber of the freeze dryer and the vent filter.*

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

----- The firm concluded that there was a “uniform temperature distribution.” No deviations were noted for the PQ validation of (b)(4)-. However for (b)(4)-, there was a technical problem with a sensor on shelf (b)(4)-, the firm decided not to repeat the measurement as there were (b)(4)- other sensors with a uniform temperature distribution. Revalidation is ----- (b)(4) ----- challenge.

- d. *Please provide summary measurements with acceptance criteria for freeze drying process, sterilization (with cool down), integrity testing (filter, process, vacuum), and system performance.*

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

- e. *Please provide summary validation measurements with acceptance criteria for evacuation time and leak rate.*

The evacuation time and leak rate were tested during OQ with the following results.

[(b)(4)]

There are differences observed between both parameters. Lyo (b)(4)- has a higher leak rate and a longer evacuation time.

- f. *Please provide temperature measurements of shelves and product, and differences between temperature measurements of shelves and product obtained during validation.*

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

The product temperature probes (n=(b)(4)-) are used only for monitoring of the cycle and do not influence the freeze drying cycle, therefore validation of the difference between the shelf temperature and the product temperature were not required.

- g. *Please provide data for the ice capacity of freeze dryers.*

The ice capacity is (b)(4)-.

- h. Please provide validation summary results of condenser temperature and cooling capacity.*

The condenser temperature and cooling capacity were tested during OQ.

[
--(b)(4)--
]

- i. Please provide procedure for how freeze dryers are cleaned including frequency and cleaning agent.*

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

- j. Please identify any other products that are lyophilized in the freeze dryers.*

- Octanate Human factor VIII concentrate
- Octanine F Human factor IX concentrate
- Octaplex Human prothrombin complex concentrate

- k. Please provide the following process validation information, for each batch and freeze dryer:*

- *Please provide the lyophilization cycle parameters (i.e. set points, range/limits) at each step of the process for temperature, time/duration, chamber pressure and vacuum including ramps.*

The information included in the amendment for each batch and freeze dryer was reviewed and found to be acceptable.

- *Please provide the T_e (Eutectic Point) and T_g (Glass Transition Temperature).*

------(b)(4)----- analysis was reported to reveal no transitions other than an exothermic transition attributable to crystallization with onset at ca. -----(b)(4)----- being consistent with eutectic measurement where a change in resistance peaking in the range of -----(b)(4)---- could be detected. Also, a eutectic melt with onset at ca. -(b)(4)- was determined.

- *Please provide loading time and the loading temperature of the shelves and product.*

Loading of the lyophilizer is conducted at a shelf temperature of -(b)(4)- with the product after filling is at room temperature -----(b)(4)-----.

- *Please provide the tray positions.*

Each used shelf of the lyophilizer is loaded with -(b)(4)- trays. All trays are filled with -(b)(4)- vials. ----- (b)(4) -----

The shelves that were used and the ones that are not used were not identified in the information provided.

- *Please provide the loading pattern and the number of vials.*

The amendment included overall information for load pattern and vials, but specific information was not provided.

- *Please identify sampling points for temperature mapping.*

The position of the temperature probes used for recording the product temperature is not specified in detail. -(b)(4)- temperature probes are available to be distributed in the chamber. The distribution is done randomly based on the actual loading pattern (no of shelves used).

- *Please provide the specifications and the number of testing failures for each validation lot for testing including cake appearance and color, broken vials, and un-stopper vials.*

The information provided was reviewed. Batch ----- (b)(4) ----- had a larger number of vacuum defects. Specifications were not provided. Cake appearance was acceptable for all batches.

- *Please provide 057SOP123 used for the freeze drying process.*

The SOP matches the freeze drying cycle parameters listed above. The SOP also states that ----- (b)(4) ----- has to be started earliest -(b)(4)- and latest after -(b)(4)- of freezing time. The drying is done automatically with the chamber aerated after drying. Unloading of the freeze dryers is done manually.

8. *For each conformance lot:*

- a. *Please provide the range of results for residual moisture--(b)(4)-----
----- after lyophilization before heat inactivation.*
- b. *Please provide the number of vials that did not meet the specification for residual moisture after lyophilization before heat inactivation.*

The requested information was included in the amendment and reviewed.

- c. *Please provide the total number of vials filled and freeze dried.*

The information was included in the amendment and reviewed.

- 9. *It was stated that the procedure for “Visual Inspection of Liquids and Freeze-Dried Products and Verification of Solubility” (130SOP006/01, dated 20 Nov. 2006) that solubility instructions stated to add WFI for dissolution time and “compare the solution with its specified appearance” however this product has a diluent different from WFI. Please provide justification and data to support the use of WFI for dissolution time and appearance.*

The SOP was reported to be misleading by just mentioning WFI and has been revised to state solvent where applicable. Procedure 130SOP006/02, entitled “Visual inspection of freeze-dried products and ----(b)(4)--- and WFI used for reconstitution and verification of solubility of freeze-dried products” was provided. The visual inspection is an ocular inspection using a screen with a black and white background after dissolution of the lyophilized product.

- 10. *Please provide procedure for visual inspection.*

The "Visual Inspection of Liquid Products (except Octaplas) and Lyophilized Products" No. 041SOP006/10 was provided. -----(b)(4)-----

----- Defects can be incorrect crimping or defect cap; defective, damaged or incorrect position stopper; glass defects (bottom, wall, shoulder, neck); missing ink-jet number; mechanical impurities or clear visible marks on the inner side of the glass; remaining lyophilized product on the stopper; varieties of color in or on the lyophilized product; crash; and defective vacuum. The criteria for defects for incidence reporting are: -----(b)(4)-----

11. Please provide in-process QC results for batches -----(b)(4)----- (900 IU/mL).

In-process control results of -(b)(4)- consecutive batches produced in 2006. There were two batches where the TVC was over the limit for sample FFP.

There was a deviation for the loss of QC sample number 0KZ for batch -----(b)(4)----. The sample was documented as being taken however could not be located in the laboratory.

12. Please provide final QC results for final product batches -----(b)(4)---- (450 IU/mL) and -----(b)(4)---- (900 IU/mL).

The results of -(b)(4)- consecutive batches were included in the amendment and reviewed.

13. Please provide translations to English for the following:

a. Batch -----(b)(4)-----, yield summary records and page 62 comments.

These were provided in the amendment and reviewed.

b. Batch ----(b)(4)-----, the beginning information of vWF/FVIII ---(b)(4)-- batch record (057HBE18x/02) and reasons for samples -(b)(4)- on page 23.

--(b)(4)-- was for analytic testing and -(b)(4)- for validation after freeze-drying. -(b)(4)- samples were for analytical testing after heat inactivation.

c. All batches for Plasma Cryoprecipitation Separation, page 29 Comments

The information was provided and reviewed.

d. All batches for Wilate-vWF/FVIII -(b)(4)-, code no. 057HBE18x/02, for printouts and additional records.

The information provided included environmental monitoring counts during filling. For batch ----(b)(4)-----, one -(b)(4)- (finger print glove) control exceeded the warning limit of ---(b)(4)---- and was identified as *Micrococcus lylae*, and one was at the lower limit for clothing contact plate, identified as *Micrococcus luteus*. For batch ----(b)(4)---, all environmental monitoring was within limits.

14. Please provide the following information missing from the batch records:

a. Temperature recordings for batches -----(b)(4)-----.

The information was provided and reviewed.

b. Page 61 for batch ----(b)(4)-----, containing steps ---(b)(4)----- (column -(b)(4)----- preparation) and -----(b)(4)-----.

The information was provided and reviewed.

15. Please provide the hold time and temperature allowed for vials during -(b)(4)- testing after lyophilization and after dry heat treatment for inactivation. Provide summary data for each conformance lot for the time and room temperature for both testing steps, which vials were at room temperature during the -(b)(4)- testing before being placed back into storage at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

There is no hold time limit defined for the vials during the -(b)(4)- testing. The -(b)(4)- testing is performed at -----(b)(4)----- . The vials are taken out of the -----(b)(4)----- prior to measurement. During this period vials are stored at -----(b)(4)----- . This is done to ensure that the vials are free from condensate on their outside surface and remaining humidity would not interfere with the measurement.

16. Please provide the procedure used for -----(b)(4)----- of product vials.

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

REVIEW COMMENTS:

1. Data reviewed for Lyophilizer -----(b)(4)----- demonstrates results for 900 IU has a variance for residual moisture of $1.2 \pm 0.37\%$ (w/w) for batch ----(b)(4)---- and $1.2 \pm 0.34\%$ (w/w) for batch ----(b)(4)----, and 68 rejects for -(b)(4)- after lyophilization for batch ----(b)(4)----, therefore -(b)(4)- may not run at the optimum conditions as robust as -(b)(4)- for the 900 IU lots. However, -(b)(4)- for 450 IU did not show the same degree of variation as the 900 IU lots. With all the validation (450 IU and 900 IU) lots conformed to the pre-set specifications for residual moisture --(b)(4)- and others tests. We would defer to the Product Office for the final decision.
2. The firm reported that -(b)(4)- columns may be used for up to -(b)(4)- cycles. The cycle number was based on small scale study and not reported under full-scale use conditions, therefore -(b)(4)- maybe excessive. The Product Office should review the number of cycles per re-use for approval. A real-time, full scale concurrent validation study may be considered to establish column lifetime use.
3. Recommend waiver of Pre-approval Inspection. See Inspection Waiver Memo.

Revised by: Marion Michaelis: 11/21-24/09