

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.

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

(b)(4)

Aseptic Processing:

Aseptic filling occurs in a class (b)(4) clean room. The sterile bulk solution is filtered into (b)(4), sterilized (b)(4) vials.

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

Filling is performed on an automatic filling line (b)(4) consisting of a (b)(4).

The batch record (b)(4), for vWF/FVIII (b)(4), page 12 of 27, step (b)(4) lists the fill sizes at 2.5 mL for 250 IU/vial, 5.0 ml for 500 IU/vial, and 10.0 mL for 1000 IU/vial. The fill weight (minimum and maximum) is calculated based (b)(4).

Results meeting specifications for FVIII: C IU/mL, (b)(4). The start and end time for filling is recorded with the number of vials and trays filled. Product residuals are collected, weighed and sent for destruction.

Container Closure Integrity (section 3.2.P.7.1):

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) -----

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

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)-----
------. 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:

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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

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)--]

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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)-----

-----.

- 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) -----

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)----- . 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.

- 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 Te (Eutectic Point) and Tg (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)-----.

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°C ± 3°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±0.37% (w/w) for batch ----(b)(4)---- and 1.2±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