



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Building 71, G112
Silver Spring, MD 20993-0002

To: DATS: 597287

STN BLA 125582/0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

From: LCDR Donald Ertel, Regulatory Officer, OCBQ / DMPQ / MRB1

Through: Carolyn Renshaw, Branch Chief, OCBQ / DMPQ / MRB1

CC Edward Thompson, RPM, OBRR/RPMS
Mikhail Ovanesov, Chair, OBRR/DHRR

Subject: DMPQ Primary Review for Original Biologics License Application filed per 21 CFR 601.2 for Coagulation Factor IX (Recombinant), Albumin Fusion Protein indicated to treat patients with hemophilia B (congenital Factor IX deficiency) for Routine prophylaxis to prevent or reduce the frequency of bleeding episodes, Control and prevention of bleeding episodes, and Control and prevention of bleeding in the perioperative setting

Applicant: CSL Behring Recombinant Facility Ag (License Number Pending)

Facility

1. (b) (4)
2. CSL Behring GmbH (CSLB) FEI # 3003098680 - Emil-von-Behring-Strasse 76 D-35041 Marburg Germany

ADD: 05 Mar 2016 (10/9/2015:Major Amendment received; 3 months added to ADD)

Conclusion and Recommendation

I recommend approval of this submission. The qualification and validation activities, as related to facility, equipment, and container closure appear adequate for the manufacture of Coagulation Factor IX (Recombinant), Albumin Fusion Protein. This is my final review memo for this submission; there will be no subsequent addendum reviews. I reviewed DMF (b) (4) for the Sterile Water for Injection, which is co-packaged with the product; the review is attached to this file.

Review Memo Format and Table of Contents

I have provided a summary of information provided in the submission that is under DMPQ purview as outlined in SOPP 8401.4: In general, my Review Assessment / Comments are provided at the end of review sections in a double lined box. Any information requests (IRs) related to review will be included in these boxes in bolded text. A summary of the firm's response to that IR will immediately follow in italicized text or in a subsequent Amendment Review memo. My assessment of the response will immediately follow in a double lined box.

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1. Amendments related to Review

- 125582/0.1 received 02 Jan 2015 to Information Request on 22 Dec 2014 (in support of Inspection Waiver Memo).
- 125582/0.3 received 11 Feb 2015 to Information Request on 09 Feb 2014 (in support of Inspection Waiver Memo).
- 125582/0.51 received 20 Jan 2016 to to Information Request on 12 Jan 2016 (for 21 CFR 25.15(d) claim)
- 125582/0.54 received on 28 Jan 2016 to Information Request on 21 Jan 2016

2. Regulatory History

The agency received the BLA in eCTD format on 05 Dec 2014. I was assigned as CMC reviewer on 08 Dec 2014. The application was appropriately filed per 21 CFR 601.2

One Inspection Waiver was submitted and approved for this submission for the (b) (4) (approved (b) (4)). CBER performed a Pre-license inspection at the CSL Behring Marburg facility in May 2015.

The following summary documents were reviewed:

- 2.2, 3 Introduction
- 2.3.A Appendices
- 2.3.P Drug Product
- 2.3.R Regional Information
- 2.3.S Drug Substance
- 2.6.1 Introduction

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3.2.A.1.4-1.1.1 Facility Layout Plan, (b) (4) Building (b) (4)
3.2.A.1.4-1.1.2 Facility Layout Plan, (b) (4) , Building (b) (4)
3.2.A.1.4-1.1.3 Facility Layout Plan, (b) (4) , Building (b) (4)
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3.2.A.1.4-1.1.6 Material Flow Plan, (b) (4) , Building (b) (4)
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3.2.P.2.1 Components of the Drug Product
3.2.P.2.2 Formulation Development
3.2.P.2.2.1 Report REP-8537, Formulation and Lyophilization Summary Development Report
3.2.P.2.2.2 REP-9774, Summary Development Report for 250 & 2000 IU DP Dosage Forms
3.2.P.2.2.3 Report 010200017, Optimization of the Lyophilization Procedure for the 2000 IU DP Dosage Form
3.2.P.2.3 Manufacturing Process Development
3.2.P.2.3-1 Report RA-809-002-03, Detailed Potential Failure Modes and Effects Analysis
3.2.P.2.3-1 Report SR-809-001-03, CSL654 (rIX-FP) DP Process Justification Report
3.2.P.2.4 Container Closure System
3.2.P.2.5 Microbiological Attributes
3.2.P.2.5-1 Summary Report MF-(b) (4)-051-01, Routine Re-Validation of Aseptic Processes by Media Fills in the Filling Area (b) (4)
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- 3.2.P.3.2 Batch Formula
- 3.2.P.3.3.1 Drug Product (DP) Manufacturing Process Flow Diagram
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- 3.2.P.3.3.3 Reprocessing
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- 3.2.P.3.4.2 In-Process Methods and Method Validation Status
- 3.2.P.3.4.3 Control of Critical Intermediates
- 3.2.P.3.5.1 Introduction to Process Validation Summary
- 3.2.P.3.5.1.1 Report SR-809-003-01, Validation Overall Summary for DP
- 3.2.P.3.5.10 Final (b) (4) Validation
- 3.2.P.3.5.11 Continued Process Verification
- 3.2.P.3.5.11.1 Report 920606-01, Trending of Relevant Parameters for rIX-FP DP Manufacture as Part of Continued Process Verification
- 3.2.P.3.5.2 Process Control Strategy
- 3.2.P.3.5.3 Process Performance Qualification
- 3.2.P.3.5.3.1 Report PV-809-011-02, PPQ of the Production Process for rIX-FP DP in the production area (b) (4) and in the Filling and Lyophilization area in (b) (4)
- 3.2.P.3.5.3.2 Report PV-809-014-01, PPQ of the Lyophilization of rIX-FP CSL654
- 3.2.P.3.5.4 Filling Validation
- 3.2.P.3.5.4.1 Report PV-809-04-02, Process Validation for the Filling Process of rIX-FP 500IU
- 3.2.P.3.5.4.2 Report PV-80905-01, Process Validation for the Filling Process of rIX-FP 1000IU
- 3.2.P.3.5.4.4 Report PV-809-07-01, Process Validation for the Filling Process of rIX-FP 250IU
- 3.2.P.3.5.5 Lyophilization validation studies
- 3.2.P.3.5.5.1 PV-809-21-01, Lyovalidation of CSL 654 250IU -Freeze Dryer (b) (4)
- 3.2.P.3.5.5.2 PV-809-022-01, Lyovalidation of CSL 654 500IU - Freeze Dryer (b) (4)
- 3.2.P.3.5.5.3 PV-809-23-01, Lyovalidation of CSL 654 1000IU - Freeze Dryer (b) (4)
- 3.2.P.3.5.5.4 PV-809-24-01, Lyovalidation of CSL 654 2000IU -Freeze Dryer (b) (4)
- 3.2.P.3.5.5.5 Report FR-809-010-01, Feasibility of Lyophilization of rIX-FP / CSL654 250IU using Freeze-Dryers (b) (4) in Building (b) (4)
- 3.2.P.3.5.5.6 Report FR-809-011-01, Feasibility of Lyophilization of rIX-FP / CSL654 500IU using Freeze-Dryers (b) (4) in Building (b) (4)
- 3.2.P.3.5.5.7 Report FR-809-012-01, Feasibility of Lyophilization of rIX-FP / CSL654 1000 IU using Freeze-Dryers (b) (4) in Building (b) (4)
- 3.2.P.3.5.5.8 Report FR-809-013-01, Feasibility of Lyophilization of rIX-FP / CSL654 2000 IU using Freeze-Dryers (b) (4) in Building (b) (4)
- 3.2.P.3.5.6 (b) (4) Validation Results
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- 3.2.P.3.5.8 Hold time validation
- 3.2.P.3.5.9 (b) (4) Validation
- 3.2.P.3.5-4.3 Report PV-809-006-02, Process Validation for the Filling Process of rIX-FP 2000IU
- 3.2.P.7.1 Container Closure System
- 3.2.P.7.2.1 (b) (4) 6 ml vial (b) (4) glass per (b) (4)
- 3.2.P.7.2.2 (b) (4) 10 ml vial ((b) (4) glass per (b) (4)
- 3.2.P.7.2.3 (b) (4) Bromobutyl rubber stopper (b) (4)
- 3.2.P.7.2.4 (b) (4) Combination cap
- 3.2.P.7.2.5 (b) (4) Combination cap

3.2.P.7.2.6 (b) (4) Combination cap
3.2.P.7.2.7 (b) (4) Combination cap
3.2.P.7.3.1 Quality Control Procedure Q-00R, Containers made of tubular glass
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3.2.P.7.4 Container Closure Integrity
3.2.P.7.4.1 Report PM-2013-10-II, (b) (4) test
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3.2.P.8.1 Stability Summary and Conclusions
3.2.P.8.1-1 Report SR-809-008, Statistical Evaluation
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3.2.S.2.2.6 Conditions of Use and Re-Use of Materials
3.2.S.2.5.1 Introduction to Process Validation Approach
3.2.S.2.5.1.1 Process Validation Overall Summary SR-809-005-01, (b) (4)
3.2.S.2.5.1.2 Process Validation Overall Summary SR-809-002-01, (b) (4)
3.2.S.2.5.2 Process Control Strategy
3.2.S.2.5.3 Process Performance Qualification
3.2.S.2.5.3.1 Report VR-4703-01-SR, PPQ of (b) (4) CSL654 BDI Manufacturing Process Cell Culture Operations
3.2.S.2.5.3.2 Report VR-4703-02-SR, PPQ of (b) (4) CSL654 BDI Manufacturing Process ((b) (4) Purification Operations
3.2.S.2.5.3.3 Report PV-809-010-02, PPQ of the Production Process for rIX-FP DS in the Production Area (b) (4)
3.2.S.2.5.4 Continued Process Verification
3.2.S.2.5.4.1 Report CH-PVP-002.00, Continued Process Verification of the (b) (4) CSL654 (b) (4) (b) (4)
3.2.S.2.5.4.2 Report 920608-01, Trending of relevant Parameters for rIX-FP DS Manufacture as Part of Continued Process Verification
3.2.S.2.5.5 Ancillary Studies
3.2.S.4.1 Specification
3.2.S.4.4 Batch Analyses
3.2.S.4.5 Justification of Specification
3.2.S.6.1 Container Closure System

- 3.2.S.6.2 Suitability of Container Closure
- 3.2.S.7.1 Stability Summary and Conclusions
 - 3.2.S.7.1.1 Stability Report REP-11555
 - 3.2.S.7.1.2 Stability Report REP-11559
 - 3.2.S.7.1.3 Final Stability Report REP-12064
 - 3.2.S.7.1.4 Process Validation Report PV-809-025-02, Stability Study for the rIX-FP DS
 - 3.2.S.7.1.5 Interim Report IR-809-019-01, Stability Study for the rIX-FP Drug Substance manufactured in the (b) (4) Production area and stored in (b) (4)
 - 3.2.S.7.1.6 (b) (4) Study
 - 3.2.S.7.1.6.1 Summary Report REP-15440-02, (b) (4)
- 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
- 3.2.S.7.3 Stability Data

3. Environmental Assessment

CSLB is claiming an exemption from the requirement for preparing an environmental assessment for this BLA for rIX-FP, based upon 21 CFR 25.31(c) which allows a categorical exclusion for an action on an application for marketing approval, for marketing a biologic product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. CSLB confirms that to their knowledge, no extraordinary circumstances exist.

rIX-FP is a purified protein produced by recombinant DNA technology, generated by the genetic fusion of albumin to recombinant coagulation factor IX. The genetic fusion of the cDNA of human albumin to the cDNA of human coagulation factor IX enables the protein to be produced as a single recombinant protein and assures product homogeneity by avoiding chemical conjugation. The recombinant factor IX portion is identical to the Thr148 allelic form of plasma-derived factor IX. The cleavable linker between the recombinant factor IX and albumin molecules is derived from the endogenous “activation peptide” in native factor IX. rIX-FP remains intact in the circulation until factor IX is activated, whereupon albumin is cleaved off, releasing activated factor IX (FIXa) only when it is needed for coagulation. Albumin is a natural, inert carrier protein in plasma with a long half-life of approximately 20 days that is not involved in immune defense or immune response. Genetic fusion of recombinant coagulation factor IX with albumin extends the half-life of factor IX.

The active ingredient, rIX-FP, is obtained by biotechnological manufacture from Chinese hamster ovary (CHO) cells.

| |
|--|
| Review Assessment / Comments: I am in agreement with the CE. |
|--|

4. Product and Overall Process

The active ingredient in CSL654 (internal company code) is a “recombinant fusion protein linking coagulation factor IX with albumin” (rIX-FP). It is expressed and secreted by CHO cells under controlled cell culture conditions, and purified to Drug Substance (DS) via a

(b) (4), virus inactivation/filtration, and (b) (4) steps. The DS is subsequently formulated, vials are filled, and lyophilization is performed to produce DP.

During the manufacturing process there are two dedicated virus reduction steps, solvent-detergent (b) (4). In addition to the two dedicated steps, (b) (4) (b) (4) has demonstrated highly effective removal of potential viral contaminants. The steps ensure the DS is virtually free of adventitious agents.

The CSL654 drug product is a preservative-free, (b) (4) sterile filtered, lyophilized formulation presented in four fill sizes of 250, 500, 1000 and 2000 IU, and three dosage strengths (100, 200 and 400 IU/mL). The fill sizes are presented in single-use glass vials of 6 mL (250, 500 and 1000 IU) or 10 mL (2000 IU) nominal capacity. The active pharmaceutical ingredient, rIX-FP, is formulated in a (b) (4) containing stabilizers and a (b) (4).

The lyophilized DP is presented as a pale yellow to white (b) (4) plug. The proposed storage conditions are 2 to 25 °C and out of direct sunlight. Reconstitution of the DP is conducted at room temperature using a vial of sterile Water for Injection (DMF (b) (4) and a needle- less Mix2Vial™ transfer set (510K #K031861, 2003).. The DP vials are stored (b) (4) to drive the transfer of the WFI to the DP vial. Complete dissolution of the solid occurs in less than (b) (4). Following reconstitution, the liquid DP appears as a clear solution, yellow to colorless in appearance and free of visible particles.

CSL654 is intended for intravenous injection. CSL654 is a novel therapeutic with a prolonged half-life for the prophylaxis and treatment of bleeding in Hemophilia B patients.

The DS manufacturing process is conducted at two sites. The first stage of manufacture is conducted at (b) (4) and the second stage at CSLB (b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

Drug Product at CSLB

DS from Step ^{(b) (4)} is the starting material for the CSL654 DP manufacturing process. The DS is stored (b) (4)

1 Page determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

Step (b) (4) Labeling and Packaging

Labeling and packaging takes place in building (b) (4). Unlabeled vials (semi-finished product) are labeled by machine. Labeling and packaging of semi-finished product and WFI takes place at (b) (4). Components for finished product are utilized after release by quality control.

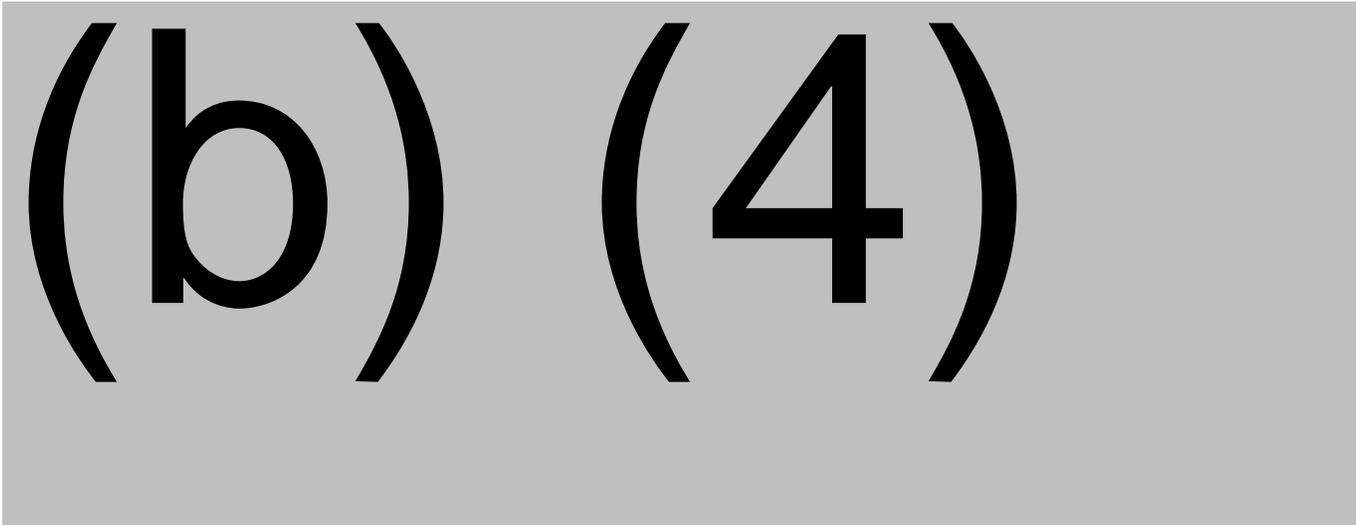
Each new batch of rIX-FP DP is assigned the next consecutive unique identifying number. The cartons are transferred to a temperature-monitored 2 – 8 °C storage facility. The Electronic Batch Recording System includes online check and verification of all packaging components.

Summary:

| Facility | Description |
|-----------------|---|
| (b) (4) | (b) (4) |
| CSLB Marburg | (b) (4) |
| | Step (b) (4) Formulation and Sterile Filtration |
| | Step (b) (4) Filling |
| | Step (b) (4) Lyophilization |
| | Step (b) (4) Capping and Crimping |
| | Step (b) (4) Labelling and Packaging |

5. Overall Manufacturing and Testing Facilities

The facilities involved in the manufacture and testing of rIX-FP are listed below along with a short description of their manufacturing responsibilities and an indication if an inspection was performed.



| CSL Behring GmbH (CSLB) FEI # 3003098680 Emil-von-Behring-Strasse 76 D-35041 Marburg Germany | | | | |
|---|------------------------------------|---|-------------------------------|-------------------------------|
| Manufacturing/ Testing activities | Inspection/ Waiver Required? | Compliance Check Required for Approval? | RMS-BLA Entry Required? | Comments |
| Drug Substance Manufacturing: fermentation, harvesting, purification, | Yes | Yes | Yes | *PLI performed in May 2015 |
| Drug product manufacturing: Lyophilization, fill and finish | Yes | Yes | | |
| Labeling/packaging | N/A* | Yes | | |
| Final release testing of drug product | Yes | Yes | | |
| Component testing (vials, water quality, environmental monitoring samples, etc.) | No | No | | |
| Diluent manufacturing “Sterile Water for injection” | No | No | | |
| Testing of (b) (4) : Contamination check (microbial growth) by (b) (4) | No | No | | |
| Stability testing and storage of samples | No | No | | |
| Storage of drug substance and drug product | No | No | | |

(b) (4)

6. CSLB Facility (Drug Substance and Product)

| Facility | Description | |
|-----------------|-------------------------|------------------------------------|
| (b) (4) | (b) (4) | |
| CSLB Marburg | (b) (4) | |
| | Step ^{(b) (4)} | Formulation and Sterile Filtration |
| | Step ^{(b) (4)} | Filling |
| | Step ^{(b) (4)} | Lyophilization |
| | Step ^{(b) (4)} | Capping and Crimping |
| | Step ^{(b) (4)} | Labelling and Packaging |

a. Facilities Overview

Production and quality control of rIX-FP Drug substance and CSL654 Drug product is performed at the CSL Behring production site in Marburg (Germany). The manufacturing site is licensed by the local health authority for the manufacture of pharmaceuticals. According to CSLB, the methods / procedures used in the manufacture, processing, packaging, labeling and

distribution of the pharmaceuticals are in conformance with cGMP, and all operations are conducted in compliance with applicable environmental laws and regulations. Regular inspections are carried out by the national competent authority to ensure cGMP compliance according to EU standards.

Multiple buildings are utilized for the production process and storage of the DS and DP of CSL654 as follows:

The facilities relevant to manufacturing, testing, and storage of rIX-FP at CSLB are as follows:

| Building | Manufacturing Operation/Testing | Relevant Floors |
|----------|---------------------------------|-----------------|
| (b) | (4) | |

(b) (4)



| 



(b) (4)

[Redacted]

Review Assessment/comments: CSLB provided illustrations of the general facility layout plan and the environmental classification plan for the relevant floors. DMF(b) (4) for Sterile Water for Injection diluent will be reviewed in a separate memo (attached to this file). No objectionable findings noted

Facility Flow Patterns

Personnel Flow:

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

Review Assessment / Comments: CSLB provided diagrams for all referenced flows. The diagrams appear to correspond with the description in the supplement. No tortuous paths appear evident, no objectionable findings noted.

b. Contamination Control

CSLB states that the facilities utilized in the production of CSL654 are designed and constructed to provide appropriate material, product and personnel flows.

After each use, production equipment is cleaned. Complete manual or automatic cleaning is performed according to written, validated cleaning procedures. Final equipment (b) (4) are performed with (b) (4). Furthermore, equipment is sterilized, depyrogenized, and/or sanitized, as appropriate.

An environmental monitoring program is established to maintain the respective clean room classifications.

Manufacturing areas and procedures utilized in the manufacturing of CSL654 are designed to maintain segregation and to prevent cross-contamination of product by appropriate clean room design using suitable material of construction and dedicated personnel and material airlocks, or adequate pressure differentials and air change rates between rooms of different classification and control by appropriate routine monitoring programs.

Production processes are performed according to cGMP regulations and include process steps to reduce or remove microorganisms and viruses. The production processes are tightly controlled by specified process control parameters and monitored by appropriate in-process- tests concerning microorganisms. Production processes have been investigated and validated concerning their efficiency to reduce microorganisms and viruses.

(b) (4)

sterile filtration of the (b) (4). Afterwards aseptic filling, validated by media fills, is performed and the product is freeze-dried. The Drug Product specification includes testing for sterility and endotoxins according to compendial standards providing assurance of the safety of CSL654 to patients. Ingredients, auxiliary substances, and excipients added during the manufacturing process are tightly controlled regarding contamination by microorganisms and their metabolites.

According to CSLB, the following general contamination / containment controls are in place:

- According to manufacturing steps respective clean room classes are established.
 - (b) (4) Clean areas for carrying out less critical steps in the manufacture of sterile products are classified as Class (b) (4) areas.
 - (b) (4) Filling is performed under aseptic conditions in a Class (b) (4) area.
 - (b) (4) Aseptic connections are made under (b) (4) under Class (b) (4) (critical) conditions.
 - (b) (4) The background environment for Class (b) (4) zone is classified as Class (b) (4) area.
- Routine monitoring according to the respective clean room classification is performed in operation.
- Compressed air is (b) (4) [at least of the quality Class (b) (4) ((b) (4) and free from (b) (4)].
- Walls and ceilings are properly sealed.
- Floors and walls are smooth, free of pores, abrasion proof, resistant to cleaning agents and anti-static.
- All room components can be cleaned easily.
- Air locks separate areas of different room classifications. Protective apparel is used and changing room procedures are established. Material/equipment is brought into the production area via air locks, where appropriate disinfection of the material/equipment is performed.
- Air handling units are designed to provide high microbial and particulate quality. HEPA filtered air with laminar flow is maintained in critical Class (b) (4) areas.
- The different production areas are supplied by unique, segregated HVAC units.
- Room differential pressures are balanced to achieve a pressure drop / airflow from higher to lower classified areas and are monitored and recorded.
- Adequate air change rates are established.
- Employee movement between critical and support areas is restricted.
- Equipment cleaning is performed following written, validated procedures.
- High quality water that meets (b) (4) specifications for (b) (4) of equipment and containers is used.
- • Equipment cleaning procedures are validated for effective removal of product and cleaning agents.
- Wherever possible, dedicated equipment is used for manufacturing.
- Room cleaning and disinfection is performed following written procedures and a clean room class related cleaning schedule is in place.
- For the aseptic filling process multi used filling equipment and filling needles, which are dedicated for rIX-FP are used; filling hoses, seals, and aseptic connection devices are single use material
- Waste is disposed of in a manner to prevent contamination or confusion.
- Staff is routinely trained prior to participating in manufacturing operations. In addition training regarding SOPs, hand washing, putting on gloves, and gowning procedures are performed on a regular basis.
- Well-run preventive maintenance programs provide information regarding the life cycle of facility systems and equipment, before failures stop production.

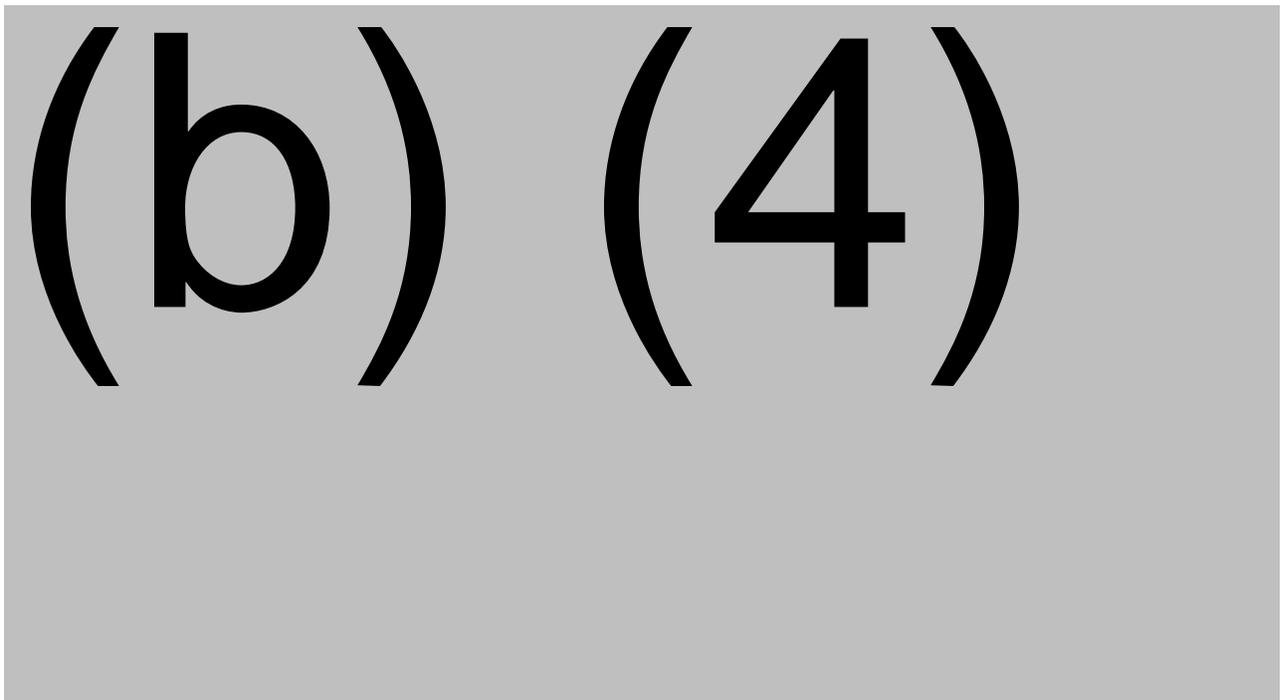
- The manufacturing process includes appropriate controls to assure that product will not be contaminated during processing (e.g. validation of sterilization/depyrogenation of all equipment and components associated with regard to endotoxin and microbial bioburden).
- Change Control System is in place.

Review Assessment / Comment: Standards practices for prevention of cross-contamination appear to be in place. No objectionable finding noted.

c. General Cleaning and Disinfection

According to CSLB, the cleaning and disinfection process in the production areas including cleaning and disinfection frequencies (based on Standard Operating Procedure SOP 520176), listing of the surfaces to be treated and the documentation of the cleaning and disinfection processes is specified in area specific SOPs. Their SOP 520176 “*Approved disinfection and cleaning agents for room hygiene*” lists validated disinfection agents for room disinfection and regulates general cleaning and disinfection items like concentration of disinfectant agents and contact times.

As determined in disinfectant efficacy validation studies (Final Report of Validation No. QCMO-0204 and QCMO-0297), CSLB established the holding time and concentration of the tested disinfectant agents as follows:



The validation of the disinfectants listed in SOP 520176 was performed according to the

(b) (4)

A selection of surface materials, which are found in the production areas, was included in the validation.

The following microorganisms were used as test organisms: (b) (4)

According to CSLB, the effectiveness of the applied disinfection procedures and disinfectants is demonstrated under routine production conditions by an environmental monitoring program.

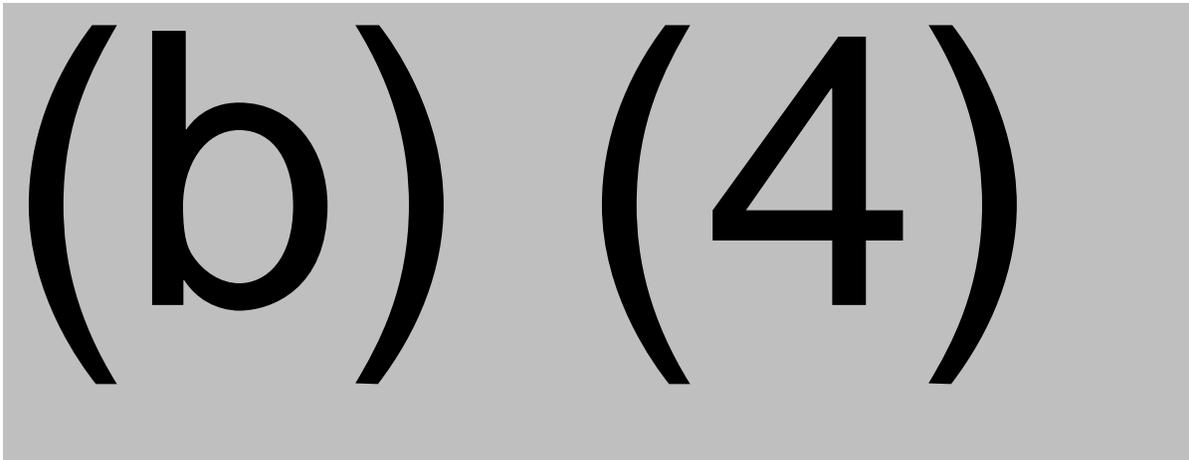
(b) (4) is used in all production areas as cleaning agent. In addition to the neutral cleaning agent (b) (4) a special surface cleaner, (b) (4) is used as particular application in the case of protein residues on floors in clean rooms classified as class (b) (4)

Cleaning and disinfection are carried out in accordance with detailed hygiene schedules. The required procedure and frequency is given in specific SOP's or programs for each production area. The hygiene measures for rooms include the cleaning and disinfection of floors, surfaces (e.g. work bench, external surfaces of machines), walls and ceilings, furniture (e.g. cupboard), sinks and drains. According to CSLB, Class (b) (4) rooms, Class (b) (4) rooms, Class (b) (4) rooms are cleaned (b) (4) working day, and disinfected (b) (4)

Review Comments/ Assessment: Cleaning and disinfection practices for the facility appear to be adequate for their intended use. No objectionable finding noted.

d. Pure Steam in Building (b) (4) 9

An overview of the Pure Steam System in (b) (4) is as follows:



(b) (4)

(b) (4)

Review Assessment/Comments: No objectionable findings noted.

e. Water Systems

PUW Building (b) (4)

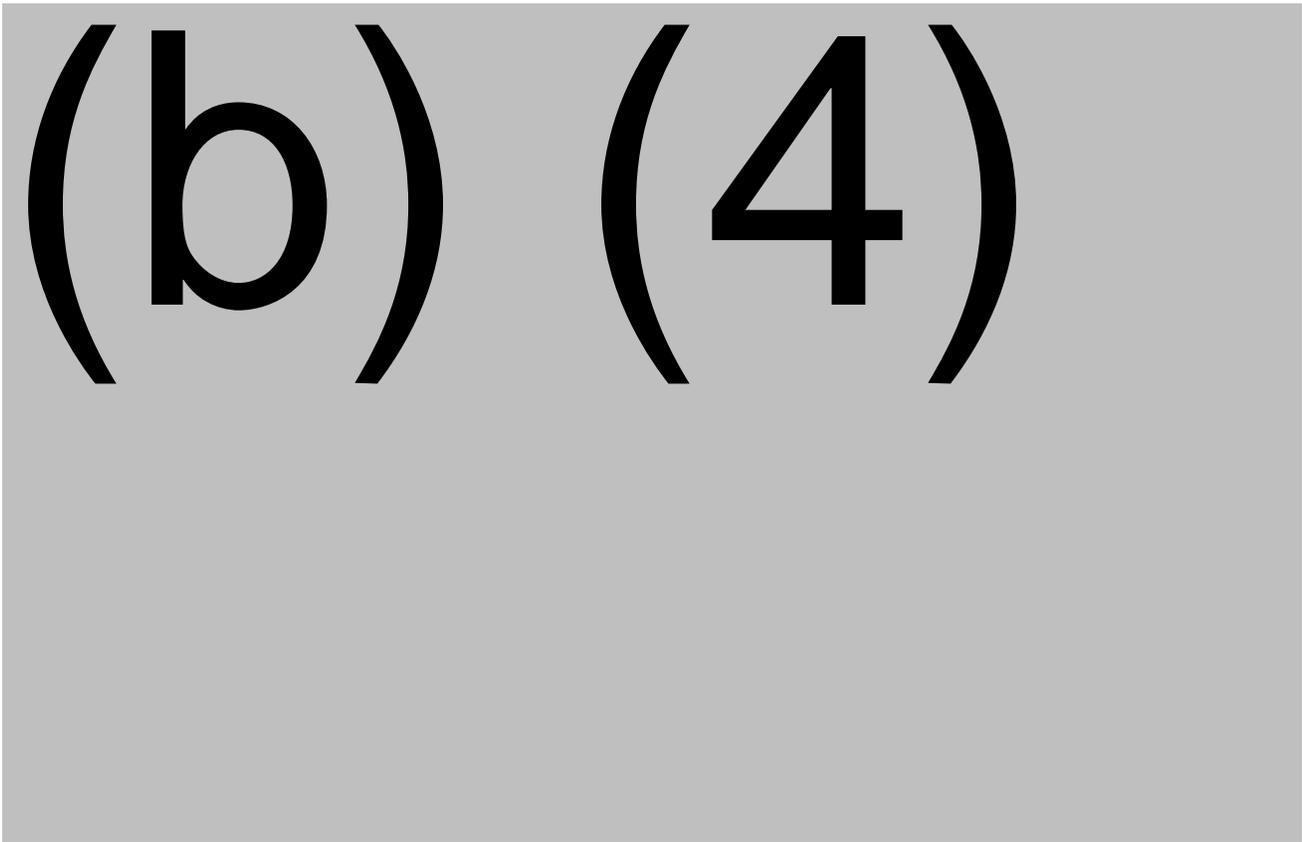
(b) (4)



| Tests | Acceptance Criteria |
|---------|---------------------|
| (b) (4) | (4) |

WFI in Building (b) (4)

Purified Water (PUW) is used as (b) (4) water for the generation of WFI. The WFI generation system consists of (b) (4) distillations Units (b) (4). All distillation Units produces WFI by a (b) (4) distillation process. The generated WFI is stored in (b) (4) (b) (4) that in turn supplies seven WFI storage tanks. Each of these (b) (4) supplies a WFI (b) (4). Relevant for rIX-FP production are (b) (4) (“support”) and (b) (4) BH01 (b) (4). An overview of the Water for Injection System in (b) (4) is as follows:



(b) (4)

| Room No. | Equipment |
|----------|-----------|
| (b) (4) | (b) (4) |
| (b) (4) | (b) (4) |

(b) (4)

The specification for WFI PQ and Routine Testing:

| Tests | Acceptance Criteria |
|---------|---------------------|
| (b) (4) | |

CSLB reports the performance of IQ, OQ, and PQ for the initial qualification, including the description of the tests performed and the acceptance criteria. If the initial qualification is not older than (b) (4), the data resulting from the performance tests was submitted as a Test Result Summary. If the initial qualification was older than (b) (4) data of the routine environmental monitoring over a period of at (b) (4) were submitted as Trend Reports.

CSLB reports that the results demonstrate that the installation, operation, and performance of the systems are in accordance with the acceptance criteria and in a validated state.

(b) (4)

[Redacted]

[Redacted]

Review Comments/Assessment:

CSLB provided schematics for all Water storage and distribution systems along with detail descriptions of their operation. Diagrams appear to correspond with the description. Relevant P&ID are referenced. Water systems appear to be of standard design and operation. The WFI system qualifications appear to be comprehensive with standard verifications addressed. CSLB has provided the associated qualification documents and SOPs in the submission. Acceptance Criteria appears to correlate with (b) (4) standards for WFI.

by the Manufacturing Execution System (MES).

Review Assessment / Comments: CSLB provided a technical description of the design/operation of the each HVAC system; the systems appear to be standard pharmaceutical design and operation. DP, Temperature, and Humidity specification were provided in the submission in tables for each room supplied by each HVAC unit; the specs appear to correlate with Plant drawing.

System Qualification

CSLB reports the performance of IQ, OQ, and PQ for the initial qualification, including the description of the tests performed and the acceptance criteria. If the initial qualification is not older than (b) (4), the data resulting from the performance tests was submitted as a Test Result Summary. If the initial qualification was older than (b) (4) data of the routine environmental monitoring over a period of at (b) (4) were submitted as Trend Reports.

CSLB reports that the results demonstrate that the installation, operation, and performance of the systems are in accordance with the acceptance criteria and in a validated state.

IQ included verification of:

- Equipment Calibration
- Hardware
- Wiring
- Input/output functions
- Configuration
- Instrumentation
- Software
- (b) (4) Compatibility
- Documentation
- Mechanical Installation
- Clean Room Installation
- Material Documentation

OQ included verification of:

- Equipment Calibration
- Utility
- Security and Access
- Critical Component Operation
- Configuration
- Alarm Test
- DP
- Airflow Visualization
- Critical Parameter Limiting Values Functionality
- Power Failure Recovery
- Backup Procedure
- (b) (4) Test
- Air Flow Velocity
- Air Volume / Change Rate Test
- Door Interlock Function
-

For PQ of HVAC systems, CSLB monitored classifieds clean rooms for viable particles, non-viable airborne particles, and surface microbial contaminants. PQ occurred in (b) (4) stages as follows:

(b) (4)

| Qualification Test | Test Description / Acceptance Criteria |
|--------------------|--|
| (b) | (4) |

Routine Monitoring Program

CSLB reports that they routinely monitor the (b) (4) area on the (b) (4) floor in Building (b) (4) according to SOP 525553 entitled “Routine-Monitoring-Program for the area (b) (4) building (b) (4)”. The filling area is routinely monitored according to SOP 525346 entitled “Routine monitoring program for (b) (4) area (b) (4) floor, building (b) (4) with rooms of cleanroom classes grade (b) (4)”. The filling lines, the filling area, the lyophilization area and the crimping area are routinely monitored according to SOP 525347 entitled “Routine monitoring program for filling module (b) (4) in (b) (4) floor of building (b) (4)” and SOP 525348 entitled “Routine monitoring program for filling module (b) (4) floor of building (b) (4)”.

(b) (4) testing and airborne particulate monitoring is performed according to CSL Behring limits applied for clean rooms classified as Class (b) (4) reas respectively. Limits and test frequencies for environmental monitoring in operation are described in the attached monitoring reports. Routine monitoring is performed under in operation conditions.

CSLB provided monitoring reports containing monitoring data for the classified rooms on the (b) (4) floor of Building (b) (4) and containing monitoring data of the HVAC Systems relevant for the production of rIX-FP for a (b) (4)

Review Assessment / Comments: The qualifications appear to be comprehensive with standard verifications addressed. Relevant PQ Reports are referenced in the submission. Acceptance criteria appear adequate for the intended room classifications. The data provided appears to correspond to the design specifications, in accordance with the FDA “Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – cGMP” which recommends minimum air changes per hour to be ≥ 20 . Areas appear to be adequately classified for their intended use. Differential Pressures are depicted in directions of higher grade to lower grade areas. The acceptance criteria appear to correlate with acceptable conditions in cleanroom environments according to the (b) (4) guide to good manufacturing practice Annex 1 and the FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing.

Routine Monitoring and Periodic Requalification appear adequate to support environmental control, with limits identical to validation specs. No objectionable findings noted.

g. Processing Equipment Overview

According to CSLB, the main equipment used in the manufacture of CSL654 is of appropriate design, adequate size and suitably located to facilitate operations for its intended use and for cleaning and maintenance. All production equipment utilized in the CSL654 manufacturing operations has been qualified to ensure that it is installed according to approved design specifications, regulatory codes, and the equipment manufacturer’s recommendations, and that the equipment operates within limits and tolerances established for the process.

CSLB reports that qualification studies for all major equipment have been performed following written procedures. Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), Change Qualification (CQ), and Re-qualification (RQ) have been executed following pre-approved protocols (Qualification Plans).

The main production equipment used for Drug Substance production of rIX-FP in Bldg. (b) (4)

(b) (4)

(b) (4)

h. Equipment Qualification

Note: Performance qualification of the Lyophilizers was evaluated: See Lyophilization Section [6.n.](#) of this memo

Autoclave Performance Qualification

(b) (4)

| | Equip No. | Use |
|--|-----------|-----|
|--|-----------|-----|

(b) (4)

Review Assessment / Comments: Standard approach to sterilization qualification appears evident. CSLB reports all test runs met acceptance criteria with no significant deviations. No objectionable findings noted.

i. Equipment Cleaning Validation

CSLB reports that, with exception of Lyophilizers (b) (4) all product contact equipment and parts are dedicated to rIX-FP or single-use. The main equipment with direct product contact used for production of rIX-FP in the (b) (4) and the respective cleaning methods applied are as indicated:

(b) (4)

Review Assessment/ Comments: The relevant Cleaning Validation Reports were referenced in the submission. The cleaning validation appears to provide evidence that CSLB' cleaning procedures allow for the removal of contaminants associated with previous batch and residues of cleaning agents, as well as the control of potential microbial contaminants. (b) (4) limits appear acceptable for intended use. Rationale for (b) (4) appears scientifically sound. (b) (4) limits for dedicated equipment is acceptable. Confirmed Clean and Dirty Hold times are established. No objectionable findings.

j. Process Validation

CSLB states that their Process Validation ensures compliance with cGMP in 21CFR 210 & 211, current ICH technical requirements in Q7 - GMPs for Active Pharmaceutical Ingredients, Q8 - Pharmaceutical Development, & Q9- Risk Management; European GMP Guidelines in Annex 15; FDA's process validation guideline and EMA's draft guideline on process validation. For the rIX-FP process validation, CSLB incorporates three stages, including Stage 1 (Process Design), Stage 2 (Process Qualification), and Stage 3 (Continued Process Verification). The process control strategy was determined through completion of the Stage 1 activities. All critical process parameters (CPPs), less critical process parameters (LCPPs), key process parameters (KPPs), in-process controls (IPCs), and in-process acceptance criteria (IPACs) of the rIX-FP Drug Product (DP) manufacturing process, as described in the current commercial scale manufacturing and process descriptions. CSLB summarized all parameters in their Process Justification Report (PJR) SR-809-001-02.

Based on the results for IPCs, IPACs and the evaluation of process parameters, CSLB validated the production process at full scale according to their current commercial scale manufacturing and process descriptions. Ancillary validation studies were performed for critical mixing steps, the (b) (4), cumulative hold times, buffer preparation, the filling and lyophilization process, as well as for a (b) (4).

CSLB provided the following Stage 2 Full Scale Validation Study documentation:

(b) (4)

Other Documents relevant to Process Validation are:

- **Validation master plan:** 920582-01: Validation master plan for the process validation of CSL654 (Drug Product)
- **Risk assessment report:** RA-809-002-03: CSL654 (rIX-FP) Drug Product manufacturing process parameters, detailed FMEA
- **Process justification report:** SR-809-001-03: CSL654 (rIX-FP) Drug Product Process Justification Report

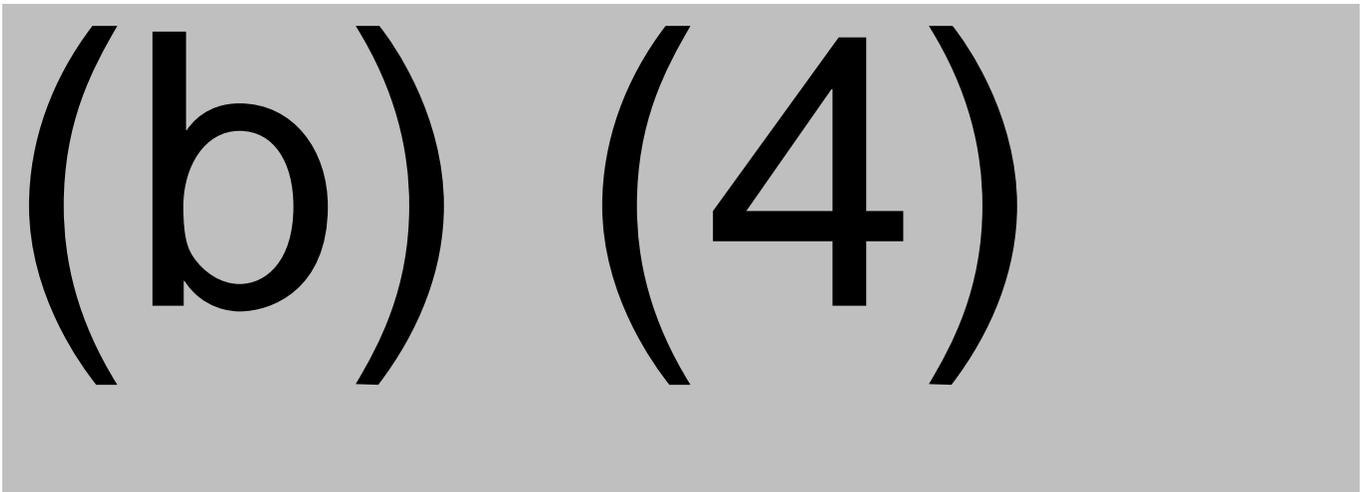
Prior to the PPQ, CSLB determined the process control strategy through completion of the Stage 1 activities. All CPPs, LCPPs, KPPs, IPCs, and IPACs in the rIX-FP DP manufacturing process, as described in the current commercial scale manufacturing and process descriptions are summarized in the PJR SR-809-001-01.

The (b) (4) was investigated at full scale; no negative effect of the (b) (4) on the product quality as well as on process hygiene was detected. The conditions for the (b) (4) process during final adjustment and for the preparation of the (b) (4) used for the (b) (4) step were investigated at full scale under worst case conditions.

CSLB performed a full scale process validation study for the cumulative hold times throughout the rIX-FP DP production process as part of the filling validation protocols. The maximum final bulk hold times at (b) (4) were additionally included in the PPQ runs. Neither a negative effect of the individual hold times nor of the cumulative hold times on the DP quality as well as on process hygiene was detected. The lyophilization processes were validated considering worst case conditions and the (b) (4) was validated at full scale.

Per RA-809-002-03, CSLB reports that they performed a FMEA for the rIX-FP DP manufacturing process parameters (RA-809-002) to evaluate all process parameters defined in the commercial scale process instructions with regard to risk of failure (i.e. operating outside of the defined operating ranges) in based on characterization work that was performed to date, the production scale historical manufacturing data to date, and the defined process outputs (i.e., IPCs, IPACs and performance parameters).

The key and high risk process parameters evaluated during DP PPQ were as follows:



(b) (4)

m. Filling (Drug Product)

Process Validation for the Filling process

- rIX-FP 250 IU, PV-809-007-01
- rIX-FP 500 IU, PV-809-004-02
- rIX-FP 1000 IU, PV-809-005-01
- rIX-FP 2000 IU, PV-809-006-02

CSLB conducted these studies to provide evidence that the aseptic filling process performed on the ^{(b)(4)} floor of building (b) (4) consistently and reproducibly delivers a homogeneous DP meeting its pre-defined acceptance criteria and quality attributes. Furthermore the hold times for (b) (4)

were validated within these studies.

The following batches were manufactured for PV for filling and Lyo:

| Strength | Batch | Filling equipment | Lyophilizer |
|----------|-------|-------------------|-------------|
| 250IU | (b) | (4) | (4) |
| 500IU | | | |
| 1000IU | | | |
| 5000IU | | | |

(b) (4)

The following objectives are covered within this validation study:

(b) (4)

(b) (4)

sual

Review Assessment/ Comments: The matrix approach to validation covering all strengths in (b) (4) filling machines and lyophilizers appears comprehensive. CSLB reports no failures to Sterility or Endotoxin testing for PPQ batches. Applicable hold times appear to have been evaluated appropriately. CSLB appears to have demonstrated that the filled units after lyophilization were homogenous from the start to the end of the filling process with respect to FIX activity and protein concentration. The final evaluation of the Product Quality Attributes is deferred to the Product Office Specialist. Furthermore, no negative effect of the cumulated hold times on CQAs of the Drug Product (lyophilized final product) was detected. Testing of the DP was performed according to Quality Control Procedure Q-809. Relevant SOPs are referenced in the protocols. No objectionable findings noted.

n. Lyophilization

(b) (4)

[Redacted]

[Redacted]

(b) (4)

Process validation (b) (4)

(b) (4)

(b) (4)

Review Assessment/ Comments: No objectionable findings noted.

p. Drug Product Release Specification

| Test | Parameter Monitored | Specification |
|--|---------------------|---------------|
| Total Protein determination by (b) (4) | Quantity | (b) (4) |
| FIX coagulation Assay | Potency Identity | |
| Albumin by (b) (4) | Identity | |
| (b) (4) | Identity | |
| (b) (4) | Identity | |
| (b) (4) | Purity | |
| (b) (4) | Purity | |
| FIXa Assay | Purity | |
| (b) (4) | Purity | |
| (b) (4) FIX activity | Purity | |
| (b) (4) | Purity | |
| (b) (4) | Purity | |
| (b) (4)-visible particles by (b) (4) | Purity | |

| Test | Parameter Monitored | Specification |
|---|---------------------|--|
| | | (b) (4) |
| Endotoxin | Purity Safety | (b) (4) |
| Sterility | Safety | Pass if no contamination detected |
| Appearance by visual inspection (Lyophilized cake) | Quality | Pass if pale yellow to white (b) (4) plug |
| Residual water by (b) (4) | Quality | (b) (4) |
| (b) (4) | Quality | (b) (4) |
| Appearance by visual inspection (Dissolution time) | Quality | (b) (4) |
| Appearance by visual inspection (Appearance after reconstitution) | Quality | Pass if yellow to colorless clear liquid and free of visible particles |
| (b) (4) | Quality | (b) (4) |
| (b) (4) | Quality | (b) (4) |
| Polysorbate 80 by (b) (4) | Quality | (b) (4) |
| Mannitol by (b) (4) | Quality | (b) (4) |
| Sucrose by (b) (4) | Quality | (b) (4) |
| (b) (4) Citrate | Quality | Trisodium citrate (b) (4) |

Review Assessment / Comments: Specifications appear to correlate with Process Validation Criteria. The theoretical maximum amount of endotoxin per dose is (b) (4). This was derived from the following calculation: (b) (4)

(b) (4)

Justification for specification for endotoxin appears acceptable but the final assessment is deferred to DBSQC and/or product office reviewer. No objectionable findings.

q. Media Simulations

(b) (4)

(b) (4)

(b) (4)

t. Container Closure

The container/closure system described here is identical to that used during final production scale development, stability studies and the media fill validations. CSLB provided stability data to demonstrate that the container closure system is suitable for the storage and reconstitution of CSL654. The CSL654 container closure system (primary packaging material) is as follows:

| Item (#) | Specifications | Description |
|--|----------------|--|
| Container 6ml (b) (4) 10ml (b) (4) | (b) (4) (4) | Vial |
| | | (b) (4) (b) (4) glass |
| | | (b) (4) |
| | | Colorless |
| Stopper (b) (4) | (b) (4) (4) | 6 mL: 250 IU, 500 IU, 1000 IU 10 mL: 2000 IU |
| | | Lyophilization stopper |
| | | Bromobutyl rubber |
| | | (b) (4) |
| Overseal (Cap) | (b) (4) (4) | Grey |
| | | (b) (4) sealing combi cap |
| | | Aluminum / Polypropylene |
| | | 250 IU: red striped / orange (b) (4) 500 IU: red striped / dark blue (b) (4) 1000 IU: red striped / green (b) (4) 2000 IU: red striped / purple (b) (4) |

With the exception of the color of the overseal, the container closure system is identical for the presentations of 250, 500, and 1000 IU, which are all filled in vials of 6 mL volume. The 2000 IU fill size uses a 10 mL vial to allow for reconstitution with 5 mL WFI, instead of 2.5 mL for the other fill sizes.

CSLB reports that the containers are single use vials made of colorless, Tubular, Type (b) (4) (b) (4) glass meeting the (b) (4) (b) (4) requirements for parenteral administration in accordance with section (b) (4) (b) (4) respectively.

The vials are closed with (b) (4) (b) (4) bromobutyl rubber stoppers that comply with Type (b) (4) requirements of (b) (4) (b) (4) and the comparable requirements of (b) (4) (b) (4) (b) (4) of the current (b) (4) (b) (4) CSL claims the formulation of the stopper does not contain natural rubber latex.

The stoppers are secured by combination caps consisting of an aluminum crimp cap with a concentric hole and an integrated polypropylene plastic disc. The crimp caps meet international standards for dimensional criteria.

;

The packaging material is accompanied by the vendor's documentation, which is controlled for each shipment. The procedures reflect current compendia requirements and the relevant national and international standards (DIN, EN, ISO), as applicable.

CSLB performs release on all primary packaging materials. According to CSL SOP, Q-00R, the inspection of injection vials of tube glass occurs as follows:

| Parameter | Specification |
|-----------|---------------|
| (b) | (4) |

(b) (4)

| Parameter | Specification |
|-----------|---------------|
| (b) | (4) |

(b) (4)

CCIT

CSLB performed CCIT for packaging material combinations associated with rIX-FP:

(b) (4)

Container closure integrity testing of the packaging material combination was performed with samples from three media fill lots with the same packing material combinations to evaluate the integrity of the vial glass body, stopper, and vial neck. A total number of (b) (4) samples from each lot were tested with the (b) (4) method using the (b) (4) test system according to testing instruction Q-52-A07.

With the (b) (4) method, the samples can be non-destructively evaluated. CSL Behring uses the (b) (4)

(b) (4)

(b) (4)

Review Assessment/ Comments: Evidence of completed CCIT study is provided, with reference to relevant protocols. No objectionable findings noted.

u. Stability

a) (b) (4)

[REDACTED]

**The date of manufacture for each CSL654 DP batch is defined as the date of final sterile filtration.

(b) (4)

b) Drug Product Stability

The proposed shelf-life of 36 months for rIX-FP for the fill sizes CSL654 1000 IU and 2000IU and 24 months for CSL654 250 IU and 500 IU under recommended storage conditions of 2°C to 25°C is supported by stability results of several initiated long term studies performed with, pilot and commercial scale batches of CSL654 manufactured during process development of the drug product.

At the time of the submission, per stability studies STR 809-003, STR 809-006, and STR 809-008, the stability claim is supported by long term real time data of 27 batches:

- CSL654 250 IU: (b)(4) batches at 18 months data and (b)(4) batches at 24 months data.
- CSL654 500 IU: (b)(4) batches at 18 months and (b)(4) batches at (b)(4) months data.
- CSL654 1000 IU: (b)(4) batches at 18 months, (b)(4) batches at 24 months and (b)(4) batches at 36 months data.
- CSL654 2000 IU: (b)(4) batches at 18 months, (b)(4) batches at 24 months and (b)(4) batches at 36 months data.

Per STR-809-PS-001, CSLB performed a photostability study according to ICH Q1B. All results were within specifications with one exception. The factor IX potency did not meet specification after (b) (4) light exposure in primary packaging. Therefore, according to CSLB, rIX-FP must be protected from light.

Data from long-term stability studies conducted with commercial scale batches at:

(b) (4)

Review Assessment/ Comments: For final DP container, sterility is tested at T₀ only. Endotoxin is tested at T₀, and 24 or 36 month test points. Container Integrity is tested at T₀, 1, 2,3,6,12,18 and 24 or 36 month test points. CSLB reports no sterility, endotoxin, or CCIT OOS up to date. No objectionable findings noted.

v. Medical transfer device

The only medical transfer device supplied with CSL654 is a transfer device used for both transfer of sterile water for injection into the product vial and filtering of the reconstituted product before withdrawal into syringe. For ease of use, the Mix2 Vial device is provided together with an alcohol swap.

Review Assessment/ Comments: The Mix2Vial device is manufactured by Medimop; I confirmed that the device is a 510K cleared since 2003 (K031861). No objectionable findings or further evaluation required.

w. Shipping Validation (BDI)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

Review Assessment/ Comments: Shipping Validation appears comprehensive and supports adequate control of product shipping temperature. No Objectionable findings noted.

x. **Shipping Validation (Drug Product)**

Per Report: TVR 5317066, CSLB validated the transport of the product from the manufacturing site to overseas.

7. (b) (4)

[Redacted]

[Redacted]

[Redacted]

| | | | |
|------------|------------|------------|------------|
| [Redacted] | [Redacted] | [Redacted] | [Redacted] |
| [Redacted] | [Redacted] | [Redacted] | [Redacted] |
| [Redacted] | [Redacted] | [Redacted] | [Redacted] |



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
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To: File DMF (b) (4)

Type II Drug Master File
Sterile Water for Injections (sWFI)

(b) (4)

[Redacted content]

12 Pages determined to be not releasable: (b)(4)