

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125795/0

recombinant ADAMTS13

Kula N. Jha, Ph.D., Biological Reviewer, MRB1/DMPQ

1. BLA#: STN 125795/0

2. APPLICANT NAME AND LICENSE NUMBER

Takeda Pharmaceuticals U.S.A., Inc., License No. 1898

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN: Recombinant ADAMTS13 (rADAMTS13)

Proprietary Name: ADZYNMA

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: Chinese Hamster Ovary (CHO) cells derived recombinant blood product, rADAMTS13 proteins
- b. Dosage form: Lyophilized powder for solution
- c. Strength/Potency: 500 IU and 1500 IU
- d. Route of administration: Intravenous injection (I.V.)
- e. Indication(s): Prophylactic or on-demand enzyme replacement therapy for patients with congenital thrombotic thrombocytopenic purpura (cTTP)

5. MAJOR MILESTONES

Filing Meeting: May 04, 2023

Mid-cycle Meeting: July 14, 2023

Late-cycle Meeting: August 31, 2023

PDUFA Action Date: November 15, 2023

6. DMPQ CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Kula N. Jha, OCBQ/DMPQ/MRB1	3.2.S Drug Substance, 3.2.P Drug Product, 3.2.A.1 Facilities and Equipment

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
March 17, 2023	STN 125795/0.0 (seq. # 0001)	Original BLA submission
April 06, 2023	Amendment STN 125795/0.2 (seq. # 0003)	The inspectional history of rADAMTS13 drug substance and drug product, and correction in FDA Form 356h Response to DMPQ information request (IR) #1 / Reviewed

Date Received	Submission	Comments/ Status
April 17, 2023	Amendment STN 125795/0.4 (seq. # 0005)	Information regarding the inspection history, FDA-approved products, and shared operations/equipment at the diluent (sWFI) manufacturing facility, (b) (4) The inspection history of drug product release testing facilities (b) (4) and Takeda Manufacturing (b) (4) Response to DMPQ IR #2 / Reviewed
May 15, 2023	Amendment STN 125795/0.9 (seq. # 0010)	Stability data for the diluent (sWFI) packaged with bromobutyl stoppers Response to OTP's IR # 1 / Reviewed
July 21, 2023	Amendment STN 125795/0.29 (seq. # 0030)	Clarification on FEI # for Takeda Pharmaceuticals (b) (4) container closure integrity testing, and aseptic filling operation Response to DMPQ IR #3 / Reviewed
September 01, 2023	Amendment STN 125795/0.36 (seq. # 0037)	(b) (4) temperature cycling stability data updated / Reviewed

Date Received	Submission	Comments/ Status
October 05, 2023	Amendment STN 125795/0.48 (seq. # 0049)	Information on the location of (b) (4) the facility for CCIT testing of the diluent (sWFI). Response to DMPQ IR # 5 / Reviewed
October 10, 2023	Amendment STN 125795/0.50 (seq. # 0051)	Clarification on sampling volume for bioburden testing. Response to DMPQ IR # 4 / Reviewed

8. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 015219	Takeda	RecombinantA DAMTS13 (rADAMTS13)	N/A	N/A
DMF (b) (4)	(b) (4)	Container closure system (CCS) information	Yes	Butyl rubber stopper (CCS) information for rADAMTS13 drug product was reviewed from the BLA.
DMF (b) (4)	(b) (4)	CCS (Vial, 8mL) (b) (4)	Yes	Glass vial (CCS) information for the diluent (sWFI) was reviewed in the BLA.

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	Rubber compound (b) (4) washing/ depyrogenation process	Yes	N/A
DMF (b) (4)	(b) (4)	Tubular glass bottles	Yes	N/A
510(k) (b) (4)	(b) (4)	Piston syringes/ (b) (4) and (b) (4) insulin syringes	Yes	N/A
510(k) (b) (4)	(b) (4)	(b) (4) winged infusion set with needle protection ((b) (4))	Yes	N/A
510(k) K092318	Baxter Healthcare Corporation	Baxject II Hi Flow Needleless Transfer Device	Yes	N/A

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Takeda Pharmaceuticals U.S.A., Inc. submitted Biologics License Application (BLA) STN 125795/0 to support the licensure of ADZYNMA, a Chinese Hamster Ovary (CHO) cell derived recombinant ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) protein. rADAMTS13 protein was developed, as an enzyme replacement therapy for thrombocytopenic purpura (TTP) patients who present severe deficiency of ADAMTS13.

The co-packaged combination product contains each of the following in a kit: package insert, 10 mL glass vial containing the sterile lyophilized rADAMTS13 drug product (500 IU/vial or 1500 IU/vial), 6 mL glass vial filled with 5 mL of the sterile water for injection (sWFI) diluent, BAXJECT II Hi-Flow Needleless Transfer Device, (b) (4) Winged Infusion Set, (b) (4) syringe (10 mL or 20 mL, respectively), and alcohol swab (pack of 2).

The Division of Manufacturing and Product Quality (DMPQ) reviewed and evaluated the rADAMTS13 drug substance (DS) and drug product (DP) manufacturing processes and

facilities proposed for the manufacture of ADZYNMA. DMPQ also assessed the manufacturing process for sterile water for injection (sWFI), the diluent used to reconstitute the lyophilized rADAMTS13 DP. This review memo includes summaries and assessments of the DS/DP/diluent manufacturing processes and quality attributes, and an overview of the DS/DP facility information including utilities, cross-contamination controls, and equipment qualification and cleaning and sterilization processes.

Following evaluations of the compliance histories, pre-license inspections (PLIs) were waived for the following DS/DP and diluent (sWFI) manufacturing, DP release testing, and DP/diluent labeling and packaging facilities:

- Takeda Manufacturing (b) (4)
(FEI # (b) (4))
- Takeda Manufacturing (b) (4) (FEI # (b) (4))
- Takeda Manufacturing (b) (4)
(FEI # (b) (4))
- (b) (4)
(FEI # (b) (4))
- (b) (4) (FEI # (b) (4))

The basis for the inspection waivers of the facilities is documented in a separate inspection waiver memo dated May 15, 2023.

Based on the information submitted to BLA 125795/0 and in conjunction with the inspection waivers granted due to favorable evaluations of FDA and/or foreign regulatory authorities inspectional compliance history, the product process, facilities, equipment, and quality controls appear acceptable for the licensure of ADZYNMA, and approval is recommended.

B. RECOMMENDATION**I. APPROVAL**

Based on the information provided in the original application and amendments, DMPQ recommends the approval of rADAMTS13 with an inspectional recommendation.

The rADAMTS13 DS is manufactured at Takeda Manufacturing (b) (4). The final formulated lyophilized rADAMTS13 DP is manufactured, filled, labeled, and packaged at Takeda Manufacturing (b) (4). The sWFI diluent is manufactured at (b) (4). The co-packaged combination product, which contains the package insert, lyophilized rADAMTS13 DP (500 IU or 1500 IU), sWFI diluent, BAXJECT II Hi-Flow Needleless Transfer Device, (b) (4) Winged Infusion Set, (b) (4) syringe (10 mL or 20 mL, respectively), and alcohol swab (pack of 2), is kitted at Takeda Manufacturing (b) (4).

CBER understands the following inspectional recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion. The inspectional recommendation is as follows:

Takeda Manufacturing (b) (4)
(b) (4), FEI # (b) (4)
1. (b) (4), (b) (5), (b) (7)(E)

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Kula N. Jha, CMC/Facility Reviewer, CBER/OCBQ/DMPQ/MRB1	Concur	
Kathleen R. Jones, CMC/Facility Consult Reviewer, CBER/OCBQ/DMPQ/MRB1	Concur	
Lori P. Peters, Branch Chief, CBER/OCBQ/DMPQ/MRB1	Concur	
Carolyn A. Renshaw, Division Director, CBER/OCBQ/DMPQ	Concur	For

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Module 3

3.2.S DRUG SUBSTANCE

The rADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) drug substance (DS) is a mixture of Chinese Hamster Ovary (CHO) cells-derived apadamase alfa (native rADAMTS13) and cinaxadamase alfa (a variant of rADAMTS13) proteins. The two rADAMTS13 isoforms differ by a single amino acid at position 23, which is glutamine in the native protein and arginine in the variant protein.

ADAMTS13 is a plasma metalloprotease that cleaves von Willebrand factor (VWF) multimers and downregulates its thrombogenic potential. Thus, rADAMTS13 protein was developed as an enzyme replacement therapy for thrombotic thrombocytopenic purpura (TTP) patients who present severe deficiency of ADAMTS13.

The DS is a (b) (4)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

***Reviewer's comment:** Please see section 3.2.A.1 for a complete list of the DS manufacturers.*



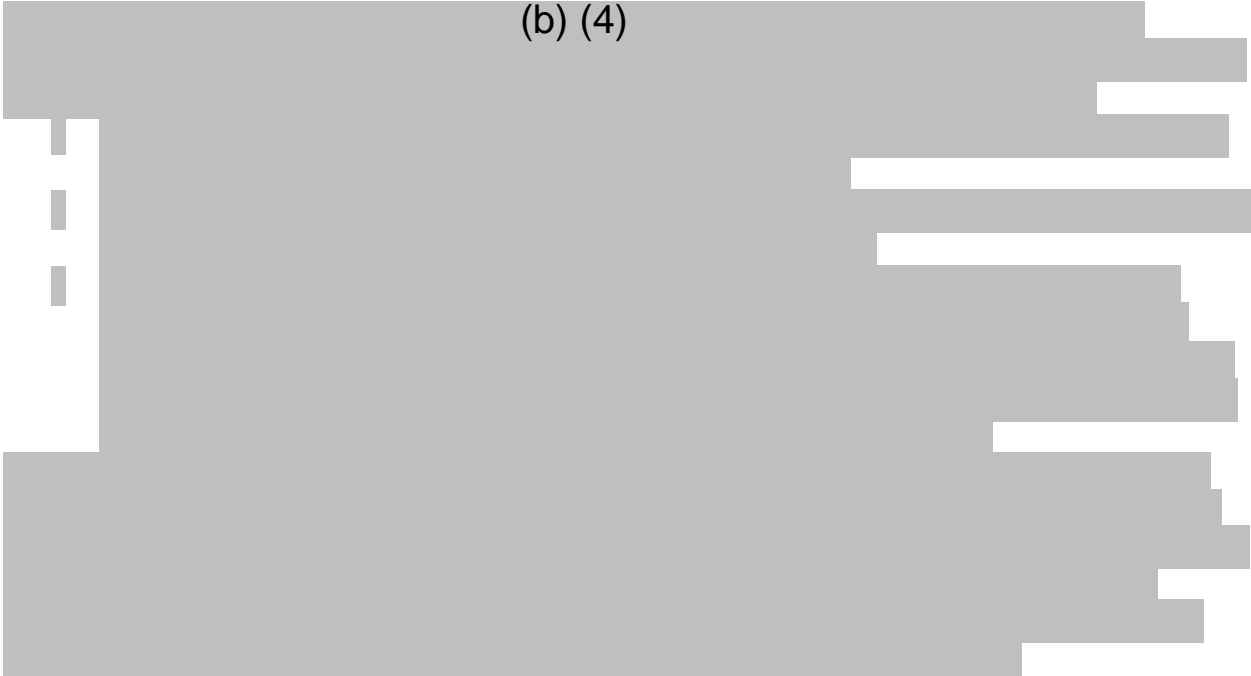
3.2.S.2.2 Description of Manufacturing Process and Process Controls

Manufacturing process steps:

(b) (4)

8 pages have been determined to be not releasable: (b)(4)

(b) (4)



3.2.P DRUG PRODUCT (rADAMTS13)

3.2.P.1 Description and Composition of the Drug Product

The rADAMTS13 drug product (DP) is formulated as sterile lyophilized powder to be reconstituted with sWFI for intravenous (I.V.) injection. The DP is filled in a primary CCS consisting of a (b) (4) grade 10 mL Type (b) (4) glass vial, a rubber stopper, and a crimp seal. Each DP vial contains a nominal dosage strength of either 500 international units (IU) or 1500 IU rADAMTS13.

One vial of rADAMTS13 DP lyophilized powder (500 or 1500 IU/vial) is co-packaged with a 5 mL diluent (sWFI) vial, a reconstitution device, a 10 mL or 20 mL syringe, a needle infusion set, and two alcohol swabs in a paperboard carton (secondary packaging).

The final dosage strength of the reconstituted rADAMTS13 DP solution is either 100 or 300 IU/mL.

3.2.P.2.5 Microbiological Attributes

Prior to aseptic filling of the final DP, the glass vials are sterilized and depyrogenated, and rubber stoppers are (b) (4)-sterilized to prevent contamination of the sterile filtered rADAMTS13 bulk. Effectiveness of the sterilization and depyrogenation procedures was verified through the media fill runs.

Container closure integrity testing (CCIT) was validated for multiple products including rADAMTS13 produced at the DP manufacturing site using (b) (4) test methods. A (b) (4) analysis method measuring (b) (4) was also used prior to release and during the shipping of the DP.

The (b) (4) test was performed by the (b) (4) method using (b) (4)

The (b) (4) test was performed by (b) (4)

100% rADAMTS13 DP vials from every manufactured lot were inspected for the presence of (b) (4) using the (b) (4) analysis method utilizing an (b) (4). The acceptance criterion of (b) (4) was indicative of an (b) (4) into the sterile DP vials.

The CCIT methods are used for the following purposes:

- (b) (4) method: initial CCI qualification
- (b) (4) test method: CCI qualification
- (b) (4): routine manufacturing, shipping qualification

- (b) (4) : stability CCIT

The stoppers used for rADAMTS13 DP were cleaned and sterilized in the stopper processor ((b) (4)), and (b) (4) cleaning runs were performed under (b) (4) cleaning conditions to assess (b) (4) reduction of endotoxin for the stoppers. Sterilization of stoppers was validated by (b) (4) runs under (b) (4) sterilization conditions ((b) (4)) and (b) (4) inactivation of the biological indicator (BI) microorganism ((b) (4)). (b) (4) was performed under routine sterilization conditions ((b) (4)), which resulted in (b) (4) inactivation of the BI microorganism.

(b) (4) sterilization and depyrogenation of the rADAMTS13 DP vials were validated by (b) (4) runs that (b) (4) sterilization conditions of (b) (4) to the routine sterilization conditions. A (b) (4) reduction of endotoxin was observed in all the (b) (4) runs.

rADAMTS13 DP release/stability specifications include microbiological quality testing for sterility, endotoxin, and CCIT ((b) (4) analysis). (b) (4) methods were used for endotoxin ((b) (4)) and sterility testing ((b) (4)).

Reviewer's comment: (b) (4) for the positive control, which is greater than the expected (b) (4) , were used for the (b) (4) study. In amendment 125795/0.29, the applicant stated that (b) (4) was selected as per (b) (4) , when the initial qualification for the CCIT was performed. The applicant further acknowledged that currently the defect size is expected to be (b) (4) but then added that the recent enhancement of the rADAMTS13 CCIT with (b) (4) test method ensures the microbial integrity of the CCS. The justification appears acceptable.

Regarding the (b) (4) test, it was unclear what (b) (4) of (b) (4) correlates too. In amendment 125795/0.29, the applicant stated that (b) (4) corresponded to a (b) (4) , which appears acceptable.

Regarding the (b) (4) analysis, it was mentioned that the (b) (4) in the DP vial must not exceed (b) (4) during routine testing. However, it was unclear what minimal (b) (4) correlates to (b) (4) . In Amendment 125795/0.29, the applicant explained that any vial with a (b) (4) below (b) (4) may have defects less than (b) (4) or no defects, which appears acceptable.

Regarding the endotoxin challenge studies, although the applicant stated a greater than (b) (4) reduction in endotoxin level was achieved upon cleaning and sterilization/depyrogenation of glass vials and/or stoppers, information on the endotoxin used and the (b) (4) amount was not provided. In amendment 125795/0.29, the applicant stated that (b) (4) bacterial endotoxin was used to (b) (4) the vials in the endotoxin challenge studies, which appears acceptable.

Additionally, it was unclear whether inactivation of BI microorganism (b) (4)) was a part of the sterilization/depyrogenation validation of the glass vials. In amendment 125795/0.29, the applicant confirmed that inactivation of the BI microorganism was included in the sterilization/depyrogenation validation of the glass vials.

DP release specification includes sterility testing but not CCIT, which appears acceptable, as CCIT qualifications using multiple CCIT methods should ensure the microbial integrity of the product filled in the container closure system. Testing and acceptance criteria for sterility and microbial controls (endotoxin and CCIT) for the DP release and stability specifications appear acceptable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Reviewer's comment: For a complete list of all rADAMTS13 DP manufacturing and testing facilities, refer to Section 3.2.A.1 of this review memo.

3.2.P.3.3 Description of Manufacturing Process

The rADAMTS13 DP manufacturing process occurs at Takeda Manufacturing (b) (4) facility.

Formulation of rADAMTS13 DP is performed in an ISO (b) (4) cleanroom. (b) (4)

(b) (4), the filters are (b) (4). The filtration of the formulated DP is performed at a defined (b) (4).

(b) (4)-sterilization integrity tests are performed on (b) (4) the filters. The filtered DP is (b) (4), and then transferred to the filling machine. Aseptic filling into vials is performed using an automatic filling machine in a Grade (b) (4) (ISO) cleanroom. Even though the filling machine (Filling Line (b) (4)) is a (b) (4) (rADAMTS13 (b) (4)), all direct product-contact parts of the filling machine are dedicated and cleaned by (b) (4) procedures. After filling, the vials are partially stoppered and subjected to the lyophilization.

At the end of lyophilization process, the stoppers are completely closed onto the vials (b) (4)

The vials are transferred from the lyophilizer to the crimping unit in a Grade (b) (4) air-supply area, and the crimped vials are transported to the warehouse.

Visual inspection is performed on 100% DP units before labeling and packaging. The labeled and packaged DP vials are stored at 2 - 8°C until shipment.

No reprocessing/reworking is permitted during the manufacturing of rADAMTS13 DP.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The CPPs or IPCs, test methods for the IPCs, and acceptable range/action limit are provided below:

(b) (4)

[Redacted content]

Based on the results from PPQ runs, the in-process hold time (b) (4) (from (b) (4)) was set as (b) (4).

3.2.P.3.5 Process Validation and/or Evaluation

The rADAMTS13 DP manufacturing process was validated either at a small scale or a full scale using the (b) (4) or product runs. The process validation utilized a (b) (4) approach with both 500 IU/vial and 1500 IU/vial dosages at (b) (4) lot size for each of the dosages. (b) (4) PPQ product lots were manufactured from which (b) (4) lots were (b) (4) after filling. Thus, (b) (4) full-scale PPQ lots were produced. However, only (b) (4) of these lots were used in the validation studies as (b) (4) was used for the lyophilization (b) (4) study. The PPQ lots are summarized below:

(b) (4)

[Redacted content]

All PPQ lots met the acceptance criteria of the validation studies, including the criteria for the sterilizing filtration, aseptic filling, lyophilization steps, and CCIT. The acceptance criteria are described below in the respective sections in this review memo. Results were provided in Table 2 (3.2.P.3.5 Process Validation and/or Evaluation – Manufacturing Process).

Lyophilization (b) (4) Study

(b) (4)

[Redacted content]

7 pages have been determined to be not releasable: (b)(4)

(b) (4)

Media Fills

The aseptic filling of the rADAMTS13 final DP was performed on a multiproduct filling line (Line # (b) (4)) within a Grade (b) (4) (ISO (b) (4)) area at the Takeda (b) (4) site. Validation of the aseptic filling operation was performed through the media fill runs simulating the routine manufacture with (b) (4)

Line # (b) (4) was requalified in 2019-21 with (b) (4) media fill runs using different vial and stopper formats. Comparable filling procedures were used for the media fill studies as that used in routine manufacture of rADAMTS13. A minimum of (b) (4) media fill runs are conducted (b) (4) and at least (b) (4) is performed under worst-case condition including maximum filling time. The batch record of the media fill runs under worst-case and routine manufacture conditions was provided in Table 24 in *Section 3.2.P.3.5 Process Validation and/or Evaluation*. All the results met the acceptance criteria and showed no microbial contamination. Some minor deviations were observed, but they did not appear to have any adverse impact on the product.

A list of standard and non-standard interventions was provided (amendment 125795/0.30), which included (b) (4)

The following acceptance criteria for the media fill simulations were provided in amendment 125795/0.30:

(b) (4)

In case of detected contamination during the media fill runs, the further courses of action include notification of management, root cause investigation, and implementation of corrective actions. If applicable, the media fills will be repeated.

Environmental monitoring (EM) is performed during each media fill operation, and the testing included microbes present in active and passive air samples, surfaces and equipment, and personnel gowns and gloves. Information on the EM parameters,

sampling location and number, and acceptance criteria were provided in Table 3 of amendment 125795/0.30.

Reviewer's comment: Line #^{(b) (4)} was requalified with the media fill runs and appears acceptable for aseptic filling of rADAMTS13. The EM as well as normal and non-routine interventions were included in the media fill simulation runs. The acceptance criteria for the media fill and proposed course of actions (in case of failure) appear acceptable.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Reviewer's comment: Please see my assessment of Specification(s) and Justification of Specification(s) in Section 3.2.P.2.5 Microbial Attributes above.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Reviewer's comment: (b) (4) methods were used for the microbiological attributes (endotoxin and sterility) of the DP. For CCIT, please see the assessment in Section 3.2.P.2.5 Microbial Attributes. Assessment of method validation testing for endotoxin and sterility for rADAMTS13 DP release is deferred to Division of Biological Standards and Quality Control (DBSQC).

3.2.P.5.4 Batch Analyses

Sterility and endotoxin test results complied with the release specifications. No deviations/discrepancies with a potential impact on the microbial quality attributes were reported.

Reviewer's comment: Information provided on the batch analyses appears acceptable. Results for all the DP lots met the specifications for sterility (sterile) and endotoxin (b) (4), which appears acceptable.

3.2.P.7 Container Closure System

The final rADAMTS13 DP is filled in a primary container closure system consisting of a (b) (4) grade 10 mL Type^{(b) (4)} glass vial, (b) (4) laminated rubber stopper with (b) (4) coating (b) (4) under the flange, and an aluminum crimp seal.

The secondary packaging material, which consists of a paperboard carton with a paperboard divider, contains one vial of rADAMTS13 DP lyophilized powder (500 or 1500 IU/vial), one vial of 5 mL diluent (sWFI), one reconstitution device, one 10 mL or 20 mL syringe, one needle infusion set, and two alcohol swabs.

Information on materials of construction of the components of the primary container closure system, manufacturers, and referenced drug master file (DMF) are provided in the following table:

Component	Materials of construction	Manufacturer	DMF	Comments
10 mL glass vial	Clear, colorless, Neutral, borosilicate glass Type (b) (4) glass	(b) (4)	(b) (4)	(b) (4) grade (b) (4)
Rubber stopper	20 mm size, gray, (b) (4) lamination on the plug and top butyl rubber with (b) (4) coating on the sealing surfaces	(b) (4)	(b) (4)	(b) (4) grade (b) (4)
Crimp seal	Aluminum crimp seal with a polypropylene snap-off cap	(b) (4)	N/A	N/A

(b) (4)

N/A - Not Applicable

Testing of each lot of the glass vials, rubber stoppers, and crimp seal is performed by the manufacturer or by contract laboratories using (b) (4) methods except identity testing which is done in-house. The components of the primary container closure system are sampled, visually inspected for component and packaging defects, and tested for dimensions per in-house specifications.

The applicant provided drawings of the components of the primary container closure system in *Section 3.2.P.7 Container Closure System*.

Reviewer's comment: *The information provided on the rADAMTS13 DP CCS appears acceptable and suitable to protect the sterile DP from microbial ingress.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The proposed shelf-life and storage condition for rADAMTS13 DP is 36 months at $5 \pm 3^\circ\text{C}$.

(b) (4) rADAMTS13 DP lots including (b) (4) PPQ and (b) (4) clinical lots were placed on stability. The samples were stored in the CCS as described in Section 3.2.P.7, and the studies are currently in-progress to assess the long-term stability of the DP.

The stability studies are conducted at the long-term storage conditions of $5^\circ\text{C} \pm 3^\circ\text{C}$, 30°C (b) (4), and (b) (4) relative humidity (RH), at the combined storage conditions of 30 months at $5^\circ\text{C} \pm 3^\circ\text{C}$ followed by 6 months at 30°C (b) (4) RH, and at an accelerated condition of (b) (4) RH. Additionally, a photostability study as well as temperature cycling studies were conducted to evaluate impact of short-term temperature excursions during shipping and handling. The pre-defined acceptance criteria for the temperature cycling studies included sterility (sterile) and endotoxin (b) (4)) at the initial (time zero), 24-, and 36-month time points, as well

as CCIT at 12, 24, and 36 months. The temperature cycling studies were performed using both 500 IU (PPQ lot # (b) (4)) and 1500 IU (PPQ lot # (b) (4)) dosages under the following storage conditions:

(b) (4)

Up to 12 months of temperature cycling data are available to date, and the results met the acceptance criteria.

A stability study on the reconstituted drug product stored for up to (b) (4) hours at room temperature (25°C) and a forced degradation stability study for the DP were also performed. Product specific parameters were evaluated during the photostability and forced degradation studies.

The long-term stability protocol included testing for sterility (sterile) and endotoxin (b) (4)) at the time zero and 24- and 36-month time points, whereas CCIT testing is performed at time zero, 12, 24, and 36-month time points. Up to 12 and 30 months of long-term storage data are available for the PPQ and clinical lots, respectively, and the results met the acceptance criteria for sterility (sterile), endotoxin ((b) (4)), and CCIT (report result in pressure reading ((b) (4))).

Reviewer's comment: Information provided on the stability studies for the rADAMTS13 DP manufactured at the Takeda Manufacturing (b) (4) facility appears acceptable limited to the sterility, endotoxin, and CCIT results. Results from the stability studies met the acceptance criteria for sterility, endotoxin, and CCIT. Sterility testing was not performed during the reconstituted DP stability study, which appears acceptable, as the reconstituted rADAMTS13 DP will not be stored for more than three hours before its administration to patients. Assessment of the photostability and forced degradation study is deferred to the OTP reviewer.

3.2.P DRUG PRODUCT [sWFI (diluent)]

3.2.P.1 Description and Composition of the Drug Product

The diluent used to reconstitute the rADAMTS13 DP lyophilized powder is sterile WFI. The primary CCS for the diluent is composed of a (b) (4) grade single-use (b) (4) Type (b) (4) glass vial, a stopper, and a crimp seal. Each vial of the diluent contains a nominal volume of 5 mL sWFI.

The applicant claimed that the specifications of sWFI comply with the (b) (4) (b) (4) , and the diluent contains no excipients.

3.2.P.2.5 Microbiological Attributes

Prior to aseptic filling, the glass vials are washed and depyrogenated, and the rubber stoppers are (b) (4) sterilized to prevent contamination of the diluent. Effectiveness of

the CCIT of the diluent was qualified at (b) (4) using the (b) (4) test method per (b) (4).

(b) (4)

The stoppers are (b) (4) sterilized in (b) (4) qualified (b) (4) at (b) (4) in (b) (4). Sterilization validation results met the acceptance criteria.

The diluent release/stability specifications include (b) (4), sterility (sterile), and endotoxin ((b) (4)). (b) (4) methods were used for release and stability testing of the diluent.

Reviewer's comment: An equal number ((b) (4)) of the sample vials were evaluated from the (b) (4) of the fill operation to assess intra-lot variability for the CCIT with the (b) (4) test method. The CCIT used to evaluate whether the primary container closure system is an effective microbial barrier appears acceptable.

Testing and acceptance criteria for (b) (4), sterility, and endotoxin for the diluent release and stability specifications followed the (b) (4), which appears acceptable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Reviewer's comment: For a complete list of all manufacturing and testing facilities for the diluent, refer to Section 3.2.A.1 of this review memo.

3.2.P.3.3 Description of Manufacturing Process

The bulk WFI is filtered through a (b) (4) filter, filled into the vials, stoppered, and crimped. The filled volume is periodically verified by (b) (4). The filled vials are (b) (4) sterilized with (b) (4) at a minimum of (b) (4), and 100% vials are inspected for particles and the liquid level.

3.2.P.3.4 Controls of Critical Steps and Intermediates

IPC testing related to microbial control during the manufacturing steps and the acceptance criteria are given below:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: Information provided on the diluent manufacturing process along with the control of critical steps and intermediates appear adequate and satisfactory. IPCs and their acceptance criteria implemented appear acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

Process validation was performed by (b) (4) and commercial scale SWFI PPQ manufacturing runs addressing the process times, lead and holding times, IPC, and release testing. The PPQ studies was performed with (b) (4) commercial scale PPQ lots of sWFI for each CCS' stopper presentation (chlorobutyl and bromobutyl stoppers). Samples were assessed to verify quality attributes of the diluent, including the microbial controls ((b) (4)). The IPC test results met the acceptance criteria. No deviations related to microbial control was observed in the PPQ studies.

Vials:

(b) (4)

Vial Stoppers:

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment: The PPQ lots were produced (b) (4) to support manufacturing consistency of the diluent (sWFI). The process validation studies as well as the process equipment qualification studies appear acceptable. The approach taken for the process validation/requalification studies appeared acceptable, and validation of the sterilization and depyrogenation of the glass vials and stoppers appear acceptable. While the applicant has not provided information on the shipping validation, vial washing validation, depyrogenation tunnel initial qualification with temperature distribution/penetration studies, or identity of the BI microorganism used for the vial stopper sterilization validation, it appears to be low risk since (b) (4) supplies (b) (4) sterilized sWFI as a diluent for other FDA approved products.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Specifications for sWFI are in accordance with (b) (4) and include (b) (4)

(b) (4) sterility (sterile), bacterial endotoxins (b) (4)

Reviewer's comment: Specifications appear acceptable. Please also see my assessment of Specification(s) and Justification of Specification(s) in Section 3.2.P.2.5 Microbial Attributes above.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Reviewer's comment: (b) (4) grade analytical methods are used in release/stability testing of the diluent. The assessment of the method validations is deferred to DBSQC.

3.2.P.5.4 Batch Analyses

Reviewer's comment: Batch analysis data for (b) (4) commercial scale lots of the 5 mL sWFI (diluent) for each type of the stoppers, chlorobutyl rubber and bromobutyl rubber stoppers, were provided. The batches (b) (4) (b) (4) with chlorobutyl rubber stopper were manufactured in June 2018, whereas the batches (b) (4) (b) (4) with bromobutyl rubber stopper were manufactured in June 2020. Information provided on the batch analyses appear acceptable. Results for WFI requirements for microbial testing (sterility and endotoxin) and testing for (b) (4) for all these batches met the acceptance criteria, which appears acceptable.

3.2.P.7 Container Closure System

The primary container closure system for the diluent is composed of a (b) (4) grade (b) (4) glass vial, a chlorobutyl or bromobutyl rubber stopper with (b) (4) coating, and a 20 mm diameter aluminum crimp cap.

Information on materials of construction of the components of the primary CCS, manufacturers, and referenced drug master file (DMF) are provided in the following table:

Component	Materials of construction	Manufacturer	Comments
6 mL Glass vial	(b) (4) vials clear glass, Type (b) (4)	(b) (4)	(b) (4)
Rubber stopper	Chlorobutyl rubber, coated stopper ((b) (4))	(b) (4)	(b) (4)
Rubber stopper	Bromobutyl rubber, coated stopper ((b) (4))	(b) (4)	(b) (4)
Crimp cap	20 mm diameter, Aluminum cap	(b) (4)	N/A
(b) (4)			

- Not Applicable

Testing of each lot of the glass vials, rubber stoppers, and crimp seal is performed by the manufacturer or by contract laboratories using (b) (4) methods except identity testing, which is performed in-house. The components of the primary CCS received at the firm is sampled, visually inspected for component and packaging defects, and tested for dimension per in-house specification. Testing for the stoppers include microbial limits and endotoxin.

The applicant provided drawings of the components of the primary contained closure system in *Section 3.2.P.7 Container Closure System*.

Reviewer's comment: *The information provided on the CCS appears acceptable and suitable to protect the sterile diluent (sWFI) from microbial ingress. Microbial testing (microbial limits and endotoxin) included in the stoppers' specification provides assurance that the stoppers are not contaminated with microorganisms, and the acceptance criteria for the microbial limits and endotoxin appear acceptable.*

3.2.P.8 Stability**3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data**

The proposed shelf-life and storage condition for the sWFI is 60 months at < 30°C and unfrozen.

The stability studies for the diluent (sWFI) packaged in the commercial container and closed with chlorobutyl rubber stopper were conducted at the storage conditions of (b) (4) RH, and at the accelerated condition of (b) (4) RH. For the diluent packaged in commercial container and closed with bromobutyl rubber stopper, the stability studies are in-progress with (b) (4) commercial scale lots for 60 months at the worst-case long-term storage condition of (b) (4) RH and for 6 months at the accelerated storage condition of (b) (4) RH.

The stability studies for the diluent packaged in CCS with chlorobutyl rubber stopper was completed; thus, up to 60-month time points data were provided. For the diluent packaged in CCS with bromobutyl rubber stopper, up to 24-month time point long-term stability data were provided and the studies were completed for them at the accelerated storage conditions. The applicant has committed to inform the Agency of any confirmed out-of- specification results within the shelf-life and storage condition. Additionally, the sponsor commits to place (b) (4) of the diluent per (b) (4) on stability study at the storage conditions of (b) (4) RH.

The long-term stability program included testing for sterility (sterile), endotoxin ((b) (4)), and CCIT (complies; only for diluent in CCS with bromobutyl stopper) at time zero and 36-, 48- and 60-month time points, whereas (b) (4) and (b) (4) at all time points. All results from the completed or ongoing stability studies for both chlorobutyl and bromobutyl stoppers, respectively, met the acceptance criteria.

Reviewer's comment: Information provided on stability studies for the diluent (sWFI) appear acceptable. Based on an assessment of available stability data for both chlorobutyl and bromobutyl stoppers, the proposed shelf-life of the diluent at ≤ 30 °C and unfrozen appears acceptable from microbial perspective.

3.2.A APPENDICES**Facility Table:**

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Facility: Takeda Manufacturing (b) (4)	Waiver	Yes	Yes	(b) (4) Surveillance ORA/OBPO VAI

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
FEI # (b) (4) DS manufacturing and release; DS release testing				
Facility: Takeda Manufacturing (b) (4) FEI # (b) (4) (Surviving FEI # (b) (4)) DS release and stability testing; DP manufacturing; DP release and stability testing; DP packaging and labeling; sWFI labeling and packaging	Waiver	Yes	Yes	(b) (4) Surveillance ORA/OBPO VAI
Facility: Takeda Manufacturing (b) (4) FEI # (b) (4) Manufacture and release testing of cell banks; DS/DP release and stability testing	Waiver	Yes	Yes	(b) (4), (b) (3) (A) GMP inspection (b) (4), (b) (3) (A) Satisfactory (b) (4) Surveillance ORA/OBPO VAI
Facility: (b) (4) FEI # (b) (4) DP release and stability testing	Waiver	Yes	Yes	(b) (4), (b) (3) (A) GMP inspection (b) (4), (b) (3) (A) Satisfactory

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Facility: (b) (4) FEI # (b) (4) Manufacture and release testing for sWFI (Co-packaged Diluent)	Waiver	Yes	Yes	(b) (4), (b) (3) (A) GMP Inspection (b) (4), (b) (3) (A) Satisfactory (b) (4) Surveillance ORA/OBPO VAI
Facility: (b) (4) FEI # (b) (4) In-process end of campaign testing ((b) (4) testing)	Not Required	No	Yes	 (b) (4) PAI/PLI ORA NAI
Facility: Takeda Manufacturing (b) (4) FEI # (b) (4) In-process end of campaign testing ((b) (4) testing)	Not Required	No	Yes	 (b) (4) Surveillance ORA NAI
Facility: (b) (4) FEI # (b) (4) DS release testing	Not Required	No	Yes	(b) (4), (b) (3) (A) Surveillance (b) (4), (b) (3) (A) VAI
Facility: (b) (4)	Not Required	No	Yes	(b) (4) Surveillance OBPO

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4) FEI # (b) (4) In-process end of campaign testing (b) (4) testing)				VAI
Facility: (b) (4) FEI # (b) (4) Stability testing for cell banks	Not Required	No	Yes	(b) (4) Surveillance CDER VAI
Facility: (b) (4) FEI # (b) (4) Storage of cell banks	Not Required	No	Yes	No FDA inspection history
Facility: (b) (4) FEI # (b) (4) Storage of cell banks	Not Required	No	Yes	(b) (4) Surveillance ORA NAI
Facility: (b) (4) FEI # (b) (4) Storage of cell banks	Not Required	No	Yes	(b) (4) Surveillance OBPO VAI
Facility: (b) (4) FEI # (b) (4) Release and stability testing for cell banks	Not Required	No	Yes	(b) (4) Surveillance ORA VAI

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Facility: (b) (4) FEI # (b) (4) sWFI stability testing	Not Required	No	No	(b) (4) Surveillance ORA VAI

(b) (4), (b) (3) (A)
; Center for Drug Evaluation and Research (CDER); FDA Establishment Identifier (FEI);
(b) (4), (b) (3) (A); Good Manufacturing Practices (GMP); No
Action Indicated (NAI); Office of Biological Products Operations (OBPO); Office of Regulatory Authority
(ORA); Sterile Water for Injection (sWFI); Voluntary Action Indicated (VAI)

Reviewer's comment: Please note that, per Form FDA 356h, the correct name for (b) (4)
" facility (FEI # (b) (4)) is ' (b) (4) '. The
original BLA application listed this facility as ' (b) (4) ' in Section 3.2.P.3.1
Manufacturer(s), which resulted in this discrepancy in the facility name.

3.2.A.1 Facilities and Equipment – Takeda Manufacturing (b) (4)

Site overview

The rADAMTS13 DS is manufactured at Takeda Manufacturing (b) (4)
(referred to as Takeda Manufacturing (b) (4)), which is a multiproduct facility.

The facility has (b) (4) production buildings with an approximate total area of (b) (4)
square meters. The manufacturing building is a (b) (4)-story building with an approximate
total area of (b) (4) . There are (b) (4) production areas ((b) (4)) in the
manufacturing building for the manufacture of all FDA-approved products, including
rADAMTS13 DS, which is currently manufactured in Suite (b) (4) only in classified production
areas/rooms. The requirements for the cleanrooms were provided in Table 1 (3.2.A.1
Facilities and Equipment – (b) (4)).

The rooms supporting the manufacturing operations were the following:

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

Reviewer's comment: *The cleanrooms and their classifications supporting the manufacturing operations of rADAMTS13 DS in Takeda Manufacturing (b) (4) appear to meet the EU (Annex 1) and ISO requirements and appear acceptable. Takeda Manufacturing (b) (4) is an approved multiproduct facility that manufactures rADAMTS13 DS in Suite (b) (4), which is the same suite that was formerly used to manufacture Coagulation Factor IX (Recombinant) (RIXUBIS, BL 125446). The facility also has experience manufacturing bulk DS for FDA approved CHO cell derived recombinant blood coagulation factors that have similar operations as rADAMTS13 DS. Therefore, it appears the cleanroom classifications are acceptable for their manufacturing operations.*

Facility cleaning and disinfection

The facility is routinely cleaned using qualified disinfectants following approved cleaning procedures. Disinfectant efficacy studies were performed to demonstrate the disinfectants are effective in the inactivation and removal of bacteria, molds, and spores. The surface disinfection tests were performed under specified conditions, including disinfectant concentrations and contact temperatures, to determine the minimum contact time with the disinfectant. All results met acceptance criteria. Routine environmental monitoring of classified rooms/areas is performed to ensure effectiveness of facility cleaning processes.

Reviewer's comment: *The applicant explained disinfectant efficacy studies were conducted to support the disinfectant concentrations, contact temperatures, and minimum contact time required for all disinfectants at Takeda Manufacturing (b) (4). While the details of the disinfectant efficacy studies were not provided, Takeda Manufacturing (b) (4) is a multiproduct facility that manufactures FDA approved products and has experience manufacturing bulk DS for FDA approved CHO cell derived recombinant blood coagulation factors that have similar manufacturing operations as rADAMTS13 DS.*

Contamination and cross-contamination control

Segregation of the rADAMTS13 DS manufacturing areas is supported by dedicated production rooms, dedicated process equipment, and dedicated heating, ventilation, and air conditioning (HVAC) systems.

Physical and procedural controls to minimize the risk of product contamination and cross-contamination at Takeda Manufacturing (b) (4) facility include the following:

- Design and layout of the facility and equipment
- Cleaning and sterilization (where applicable) of the facility and equipment per written standard operating procedures (SOPs)
- Validated cleaning processes
- Specific gowning and personnel training procedures according to room classifications
- Presence of only trained and authorized personnel in the production areas
- Labeling of materials and equipment
- Segregated personnel and materials flows

- Equipment qualification
- Environmental monitoring

The process/facility waste is treated in the wastewater treatment plant and disposed of into public sewer. The wastewater treatment plant is connected (b) (4).

Reviewer's comment: *The controls established to minimize the risk of contamination and cross-contamination appear acceptable, as this is a multiproduct facility that manufactures FDA approved products and has experience manufacturing bulk DS for FDA approved CHO cell derived recombinant blood coagulation factors that have similar manufacturing operations as rADAMTS13 DS.*

Facility flows

The rADAMTS13 DS manufacturing area floor plan and material flow diagram were provided in Figure 2 (3.2.A.1 Facilities and Equipment – (b) (4)).

Reviewer's comment: *The material flow provided in the floor diagram is (b) (4), which appears acceptable for the multiproduct Takeda Manufacturing (b) (4) facility.*

Environmental monitoring (EM) and qualification

(b) (4) runs of each 'at rest' and 'in operation' conditions for each classified production room were performed for environmental monitoring performance qualification (EMPQ). Sampling locations were determined based on an EM risk assessment, and airborne viable and non-viable particulates and viable surface microbes were evaluated. Results met the EM acceptance criteria, and no significant discrepancies were observed during the validation studies.

Routine EM is performed under dynamic (in-operation) conditions, and results are compared against the established limits for the room classification. The sampling locations for viable and non-viable particulates and viable surface microbes testing were determined from the EMPQ.

Any alert and action limit EM excursions are investigated as per the deviation procedure.

Reviewer's comment: *An EMPQ was conducted, and the applicant explained the results met the acceptance criteria. While the acceptance criteria and results of the EMPQ were not provided, Takeda Manufacturing (b) (4) is a multiproduct facility that manufactures FDA approved products, including bulk DS for FDA approved CHO cell derived recombinant blood coagulation factors that have similar operations as rADAMTS13. The EM program appears acceptable to ensure microbial and particulate control in the rADAMTS13 DS manufacturing areas.*

Utilities

HVAC system:

The HVAC systems are equipped with high efficiency particulate air (HEPA) filters that supply controlled air to the cleanrooms. The HEPA filters have a minimum of (b) (4) efficiency for removing airborne particulates and are certified/recertified per established SOP. The room pressure, air flow rate, relative humidity, and temperature are maintained in cleanrooms by dedicated air handling units (AHUs). Each AHU is designed to have continuously mixed with an appropriate amount of fresh air through make-up air handling units (MAUs). The minimum air flow rate in the cleanrooms is (b) (4), and the differential pressure between adjacent areas with different classifications is (b) (4). Temperature is maintained at (b) (4) except for cold rooms ((b) (4)). Routine monitoring is performed for viable air particles, non-viable air particles, and surface viable organisms, per established SOPs.

Diagram with HVAC systems locations and pressure differentials in cleanrooms at Takeda Manufacturing (b) (4) were provided.

Reviewer's comment: At least (b) (4) AHUs were installed in Suite (b) (4) to provide controlled environment in the classified production areas/rooms. A minimum of (b) (4) differential pressure is maintained between adjacent areas of different classification, which ensures the air flows from a higher classification to rooms of a lower classification. The HVAC systems appear acceptable. Also, Takeda Manufacturing (b) (4) is an existing multiproduct facility that manufactures FDA approved products, which formerly included RIXUBIS in Suite (b) (4) that is proposed for manufacture of rADAMTS13 DS.

(b) (4)

Water for injection (WFI) system:

The WFI system is comprised of (b) (4)

(b) (4)

Plant steam and condensate system:

There are (b) (4) boilers that supply plant steam. The steam condensate is (b) (4)

Clean steam generating system:

The clean steam generating system produces steam for the (b) (4) activities of all process tanks and associated transfer piping. The system is comprised (b) (4)

Quality of the clean steam is assessed by (b) (4) testing (b) (4) and (b) (4) testing of the (b) (4) for WFI requirements. The clean steam system is qualified and POU samplings are routinely monitored according to an established SOP.

Compressed gas systems:

The compressed air system supplies process air and instrument air to POUs in the manufacturing suites. The process air is (b) (4) before it is supplied to bioreactors and other equipment as well as for filter integrity testing and other POUs.

Process gases used in rADAMTS13 DS manufacturing include (b) (4). The gases are (b) (4) before supplying to POUs, and (b) (4) filters are installed at the POUs. (b) (4)

Compressed gas systems and/or new POUs were qualified prior to use, and they are routinely tested for (b) (4)

(b) (4) testing is only applicable for (b) (4) basis.

Computerized systems:

(b) (4) process control systems (PCS) are installed and configured for (b) (4) production processes for the manufacture of recombinant protein DS at Takeda (b) (4). Monitoring of production areas and equipment is also performed by the PCS.

Reviewer's comment: While the utilities qualification and requalification results were not provided, Takeda Manufacturing (b) (4) is an existing multiproduct facility that manufactures other FDA approved products and has experience with similar manufacturing operations as rADAMTS13 DS. Therefore, the established and qualified utility systems appear acceptable to support the manufacture of rADAMTS13 DS.

Equipment

Major product contact equipment used in the manufacture of rADAMTS13 DS are made of stainless steel, and they are shared among multiple products manufactured at Takeda (b) (4). Equipment, the process step involved, and the equipment cleaning and sterilization/sanitization methods (b) (4) were provided in Table 5 (3.2.A.1 Facilities and Equipment – (b) (4)). Equipment was qualified for their intended use to manufacture the rADAMTS13 DS.

Product-contact equipment:

Equipment	Manufacturing steps	Cleaning and sterilization/sanitization method
(b) (4)		

Equipment cleaning and sterilization/sanitization:

Large equipment is cleaned using (b) (4) procedures, whereas small equipment/parts is cleaned using the parts washer, (b) (4) procedures. Since the equipment are used for the manufacture of multiple DS, acceptance limits for cleaning were established based on all possible changeovers and carryover scenarios. The established cleaning acceptance limits are used for the cleaning validation.

Large equipment is sterilized using (b) (4) procedures, while small parts are sterilized by (b) (4). Cleaning of equipment surfaces are performed routinely in accordance with established procedures and documented.

Facility, utilities, and equipment qualification:

A risk-based approach was taken for qualifications of the facilities, utilities, and equipment at Takeda (b) (4). Equipment validation was performed according to approved protocols. Data from studies were generated, and a formal approval process was completed. Periodic reviews and requalification studies are performed to ensure that the equipment and facilities continue to operate in a validated state.

Reviewer's comment: *The critical product contact equipment and manufacturing facility appear to be qualified, cleaned, disinfected, and/or sterilized/sanitized and maintained according to the established procedures. Most of the critical product contact equipment are shared with the manufacture of other recombinant protein DS, and this appears acceptable because cleaning, sterilization, and/or sanitization procedures were validated at the existing multiproduct Takeda Manufacturing (b) (4) and the facility has experience with manufacturing bulk DS for FDA approved CHO cell derived recombinant blood coagulation factors, which have similar manufacturing steps as the rADAMTS13. The equipment information provided in this submission is in alignment with the FDA Guidance to Industry "For the submission of chemistry, manufacturing, and controls information for a therapeutic recombinant DNA-derived product or a monoclonal antibody product for in vivo use" for recombinant products. This information appears acceptable.*

3.2.A.1 Facilities and Equipment – Takeda Manufacturing (b) (4)

Site overview

The rADAMTS13 DP is manufactured at Takeda Manufacturing (b) (4) which is a multiproduct facility that manufactures approved plasma-derived and recombinant protein products. The BDS used to manufacture rADAMTS13 DP is received from Takeda Manufacturing (b) (4). The DP manufacturing process involves (b) (4), formulation, sterilizing filtration, aseptic filling, lyophilization, crimping, labeling, and packaging. Production is performed in (b) (4) Building (b) (4), whereas the quality control (QC) testing, packaging, and storage operations are performed in (b) (4) Building (b) (4). The classification of the cleanrooms associated with rADAMTS13 DP processes was provided in Table 2 (3.2.A.1. Facilities and Equipment – (b) (4)).

Reviewer's comment: *The cleanrooms and their classifications supporting the manufacturing operations of rADAMTS13 DP in Takeda Manufacturing (b) (4) appear acceptable based on the operations (e.g., aseptic filling, transfer from/into aseptic areas) performed within the rooms. Takeda Manufacturing (b) (4) is an existing multiproduct manufacturing facility that manufactures FDA approved plasma-derived biologics and recombinant protein drug products (e.g., Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (Advate, BL 125063) and has experience with manufacturing operations like rADAMTS13 DP. Therefore, the site appears acceptable for the manufacture of rADAMTS13 DP.*

Facility flows

Facility flow diagrams were provided for materials, waste, personnel, and product. All manufacturing flows are designed to segregate product lines and prevent

contamination/cross-contamination of the products. Facility flows are executed according to approved SOPs.

Reviewer's comment: *The facility flows for materials (including the active pharmaceutical ingredient) and wastes, including the aseptic processing areas, are mostly unidirectional. Facility flow for personnel appears directional, however, to prevent contamination of the product appropriate controls (e.g., airlocks and access barriers) are put in place in the cleanrooms/areas to reduce the risk of contamination of the product. Information provided for the facility flows in Takeda Manufacturing (b) (4) appears to be acceptable.*

Facility cleaning and disinfection

The equipment and facility cleaning are performed using qualified disinfecting agents, following validated cleaning procedures. The effectiveness of the facility cleaning procedures and disinfection agents is also ensured by routine EM of the production areas for viable air and surface microbial contamination and non-viable particulates.

A disinfectant efficacy study was performed to assess the disinfectants against a broad spectrum of challenge microorganisms ((b) (4)) with a defined concentration, contact time, and representative surfaces that are found within Takeda (b) (4). All results met the acceptance criteria.

Reviewer's comment: *Disinfectant efficacy studies were conducted to support the disinfectant concentrations and minimum contact time required for all disinfectants. While the disinfectant efficacy studies were not provided, Takeda Manufacturing (b) (4) is multiproduct facility that manufactures recombinant proteins drug products and has experience with the similar manufacturing operations as rADAMTS13 DP.*

Contamination and cross-contamination control

Segregation of the rADAMTS13 DP manufacturing areas is supported by dedicated production rooms, dedicated process equipment, and dedicated HVAC systems.

Physical and procedural controls to minimize the risk of product contamination and cross-contamination at Takeda (b) (4) include the following:

- Design and layout of the facility and equipment
- Cleaning and sterilization (where applicable) of the facility and equipment per written SOPs.
- Validated cleaning processes
- Specific gowning and personnel training procedures commensurate with room classifications
- Labeling of materials and equipment through a material management tracking system
- Segregated personnel, materials, equipment, and waste flows
- Equipment qualification
- Environmental monitoring
- In-process testing

- Only trained and authorized personnel are allowed in the manufacturing areas
- Dedicated airlocks are installed in the production areas

The process waste generated during the rADAMTS13 DP manufacturing operations is disposed of through the facility waste system, which is equipped with (b) (4).

Reviewer's comment: *The controls established to minimize the risk of contamination and cross-contamination appear acceptable, as Takeda Manufacturing (b) (4) is a multiproduct facility that manufactures FDA approved products and has experience with the similar manufacturing operations used for rADAMTS13 DP.*

Environmental Monitoring

The manufacture of rADAMTS13 DP at Takeda Manufacturing (b) (4) is conducted in cleanrooms that are classified according to the requirements of (b) (4) guidelines. Qualified HVAC systems provide a controlled environment in the cleanrooms.

An EM program is conducted per approved procedures and includes 'at rest' and 'in operation' conditions. Routine EM was performed at a frequency described in established SOPs, and action limits for the environmental and personnel monitoring based on the classification of the production areas/rooms were provided in Table 3 (3.2.A.1. *Facilities and Equipment* – (b) (4)).

The HVAC systems equipped with HEPA filters are designed to supply controlled air to the cleanrooms. The HEPA filters have a minimum of (b) (4) efficiency for removing airborne particulates. The room pressure, air flow rate, relative humidity, and temperature are maintained in the cleanrooms, and HVAC systems recirculate air with a defined amount of fresh air. The temperature in the cleanrooms is maintained at (b) (4), and the minimum air flow rates in Grade (b) (4) and Grade (b) (4) cleanrooms are (b) (4) and (b) (4), respectively. Relative humidity in the cleanrooms is maintained at (b) (4), while the differential pressure between adjacent areas with different classifications is (b) (4). The HVAC systems are qualified. Routine monitoring is performed for viable air particles, non-viable air particles, and surface viable organisms, per established EM SOPs.

Design criteria in terms of temperature, humidity, pressure differential, air flow rate etc. were provided in Table 4 (3.2.A.1. *Facilities and Equipment* – (b) (4)).

A diagram with the HVAC systems locations and pressure differentials in the cleanrooms in were provided.

Reviewer's comment: *Based on the action limits for environmental and personnel monitoring (airborne viable and non-viable particulates and viable surface microbes) under 'at rest' and 'dynamic' conditions, the EM program appears acceptable for ensuring adequate microbial and particulate control in the rADAMTS13 DP manufacturing areas. Differential pressure in the range of (b) (4) is maintained*

between adjacent areas of different classification, which ensures the air flows from a room with a higher classification to rooms of a lower classification. The HVAC systems installed to provide controlled environment in the classified production areas/rooms at Takeda Manufacturing (b) (4) appear acceptable.

Utilities

Water systems:

RO and WFI are used at Takeda Manufacturing (b) (4) facility. (b) (4) water is only used for (b) (4) steps and preparation of (b) (4) solutions. The monitoring and sanitization of the water systems are performed per approved procedures that describe the sampling process, locations, and test frequencies. The water tests are performed in accordance with (b) (4) requirements, and include testing for (b) (4) with the respective action limits set at (b) (4), respectively.

Reviewer's comment: Note: While the use/purpose of the WFI for the manufacture of rADAMTS13 DP and the water system qualification and requalification data were not provided, Takeda Manufacturing (b) (4) is a multiproduct facility that manufactures FDA approved products and has experience with the similar manufacturing operations used for rADAMTS13 DP.

(b) (4)

(b) (4)

Reviewer's comment: Note: While the use of the (b) (4) gas at the specific manufacturing operation was not provided, Takeda Manufacturing (b) (4) is a multiproduct facility that manufactures FDA approved products and has experience with the similar manufacturing operations used for rADAMTS13 DP.

Clean steam:

The clean steam is distributed through (b) (4) piping to various POUs. The clean steam is used for autoclaving and (b) (4) activities of all process

tanks and associated transfer piping. The clean steam quality tests are performed in accordance with (b) (4) requirements, and include testing for (b) (4)

Reviewer's comment: Clean steam is used for critical activities during the DP manufacturing process such as autoclaving and (b) (4) of all process tanks and associated transfer piping. The acceptance criteria (e.g., (b) (4)) for the clean steam test the same as those for WFI test per (b) (4), which appears acceptable.

Computerized systems:

(b) (4) critical computerized systems are used at Takeda Manufacturing (b) (4) facility:

These computerized systems were qualified for their intended use, and their validated state is maintained. Controls are in place to ensure system-managed data integrity per written procedures.

Reviewer's comment: While the utilities qualification and requalification results were not provided, Takeda Manufacturing (b) (4) is an existing multiproduct facility that manufactures other FDA approved products and has experience with similar manufacturing operations as rADAMTS13 DP. The acceptance criteria for their routine monitoring and testing appear to be in accordance with the standards and appear acceptable.

Equipment

Major equipment used to manufacture rADAMTS13 DP are shared among multiple products manufactured at Takeda (b) (4). A list of equipment along with the manufacturing process step involved, locations/room classifications, and whether in direct contact with the product was provided in Table 9 (3.2.A.1. Facilities and Equipment – (b) (4)).

Product-contact equipment:

Equipment	Manufacturing steps	Cleaning and sterilization/sanitization method
(b) (4)	Formulation of DP	(b) (4)
Sterilizing filtration unit	Sterilizing filtration	(b) (4)
Filling machine	Sterile filling	(b) (4)

Based on the risk to the product, lyophilization units (b) (4) are considered critical equipment even though they are not product-contact equipment. According to the information provided on equipment cleaning, it appears that the lyophilization units' validation studies included qualification and cleaning validation, and the cleaning validation is described in the validation protocol.

All equipment were qualified, per approved procedures, for their intended use and the potential to adversely impact product quality. The process included equipment qualification, cleaning validation, and/or sterilization validation. Equipment qualification was performed using a risk-based analysis approach to determine the required tests based on the specifications and intended use of the equipment. Cleaning validation was performed for all equipment surfaces with/without direct product contact and included a worst-case condition. Cleaning test parameters included (b) (4). Validation of sterilization processes included (b) (4) runs at worst-case conditions for (b) (4) in which the equipment was (b) (4). Placement of (b) (4) sensors were defined as part of a risk analysis based upon equipment design, the sterilization process, and accessibility. Sterilization process is revalidated (b) (4).

Cleaning and sanitization/sterilization of process equipment are performed per approved procedures by (b) (4), dry heat, and/or autoclaving. The intervals of cleaning, control of efficacy and documentation, status labeling, and hold time of process equipment were established and documented.

Reviewer's comment: *The critical product contact equipment appears to be qualified, cleaned, and/or sterilized and maintained according to the established procedures. The qualifications of the critical equipment are supported by the process validation lots, which met the established acceptance criteria. As most of the critical equipment are used to manufacture other FDA approved products and the manufacturing process for rADAMTS13 DP is like other FDA approved products' manufacturing processes at Takeda Manufacturing (b) (4), the h. information appears acceptable. The equipment information provided in this submission is in alignment with the FDA Guidance to Industry "For the submission of chemistry, manufacturing, and controls information for a therapeutic recombinant DNA-derived product or a monoclonal antibody product for in vivo use" for recombinant products. This information appears acceptable.*

3.2.A.1 Facilities and Equipment – Siegfried Hameln GmbH, Germany [sWFI]

Reviewer's comment: *The section 3.2.A. Facilities and Equipment for (b) (4), which is a sterile drug manufacturing facility and used for the production and release testing of the diluent (sWFI) for rADAMTS13 was not provided in the BLA. An assessment of Facilities and Equipment information specifically for the manufacture of sWFI for rADAMTS13 at (b) (4), Germany, does not appear to be warranted for the application as based upon the following points:*

- *The diluent produced at this facility is aseptically processed and (b) (4) sterilized*
- *Sterilization of vials and stoppers and (b) (4) sterilization of the diluent were validated and/or evaluated in this review.*
- *The manufacturer supplies (b) (4) sterilized sWFI as a diluent for other FDA approved products as well.*
- *This facility has an acceptable FDA inspectional compliance history of the*

manufacturing of sWFI.

- *In (b) (4), (b) (3) (A), an inspection was performed by (b) (4), (b) (3) (A). The inspection report was reviewed by FDA/ORR, who classified the inspection as VAI.*

3.2.R Regional Information (USA)

Combination Products

Reviewer's comment: *The rADAMTS13 DP is packaged and distributed as a combination product. One vial of rADAMTS13 DP lyophilized powder (500 or 1500 IU/vial) is co-packaged with a 5 mL diluent (sWFI) vial, a reconstitution device, a 10 mL or 20 mL syringe, a needle infusion set, and two alcohol swabs in a paperboard carton (secondary packaging). I defer the assessment of the combination product [e.g., management responsibility, design controls, purchasing controls, and corrective and preventive action (CAPA)] to the Center for Devices and Radiological Health (CDRH) consult.*