



Food & Drug Administration
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Silver Spring, MD 20993

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: Biologics License Application, STN 125795/0

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Salil K Ghosh, Ph.D	Lead Reviewer	11/09/2023		Kenneth S. Phillips, Ph.D.	
Brianna R Davis	Reviewer	10/06/2023		Simleen Kaur, M.S.	
Esmeralda A. Facundo	Reviewer	10/30/2023		Muhammad Shahabuddin, Ph.D.	

Through: Maryna Eichelberger, Ph.D.
Division Director, DBSQC/OCBQ

Sponsor: Takeda Pharmaceuticals Inc, USA

Subject: Lot-release test methods and their validations for the ADAMTS13, recombinant-krhn (ADZYNMA) drug substance (DS) and drug product (DP).

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of ADAMTS13, recombinant-krhn (ADZYNMA) and the associated analytical method validations or qualifications, were reviewed

1. Appearance ((b) (4) DP) (Salil Ghosh)
2. pH (DS and DP) (Salil Ghosh)
3. (b) (4) ((b) (4) DP) (Salil Ghosh)
4. (b) (4) (DS and DP) (Salil Ghosh)
5. (b) (4) (DS) (Salil Ghosh)
6. (b) (4) (DS) (Salil Ghosh)

7. Reconstitution time (DP) (Salil Ghosh)
8. Particulate matter (DP) (Salil Ghosh)
9. (b) (4) (DP) (Salil Ghosh)
10. Residual moisture (DP) (Salil Ghosh)
11. Polysorbate 80 content (DP) (Salil Ghosh)
12. Quantitation of Sodium and Calcium (DP) (Salil Ghosh)
13. Quantitation of Histidine (DP) (Salil Ghosh)
14. Quantitation of Sucrose (DP) (Salil Ghosh)
15. Quantitation of Mannitol (DP) (Salil Ghosh)
16. (b) (4) (Brianna Davis)
17. (b) (4) (DS) (Brianna Davis)
18. Endotoxin ((b) (4) DP) (Brianna Davis)
19. Sterility (DP) (Brianna Davis)
20. Identity ((b) (4) DP) (Esmeralda Facundo)
21. Residual Host Cell Protein ((b) (4)) (Esmeralda Facundo)

Conclusion: The analytical methods and their qualifications reviewed for rADAMTS13 (ADZYNMA) DS and DP were found to be adequate for their intended use.

Documents Reviewed

Information in sections of the original submission that describe control of DS and DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validation of these analytical procedures were reviewed.

Background

A new BLA (STN#125795) was submitted by Takeda Pharmaceuticals for ADAMTS13, recombinant-krhn (ADZYNMA), for use as a prophylactic or on-demand enzyme replacement therapy for patients with congenital thrombotic thrombocytopenic purpura (cTTP), also referred to as congenital ADAMTS13 deficiency. ADZYNMA is a lyophilized formulation of recombinant ADAMTS13 (rADAMTS13, active ingredient) intended for intravenous administration after reconstitution. A Chinese Hamster Ovary (CHO) mammalian expression system in a plasma protein-free milieu is used to manufacture the rADAMTS13 protein. This product is a mixture of two chemically distinct protein species (one amino acid difference) with a defined ratio range which is monitored throughout the production.

(b) (4) DS is (b) (4) to prepare the DP. The FB contains excipients such as sodium chloride, L-Histidine, Sucrose, Mannitol, Calcium Chloride, polysorbate 80 etc. After adding the target FB to the DS, it goes through sterilizing filtration, sterile filling, lyophilization and crimping to produce the final DP. The DP is a lyophilized sterile product containing either 500 or 1500 IU/vial for injection after reconstitution in 5 mL sterile water for injection.

Review Narrative

1. Appearance ((b) (4) DP)

Introduction

The appearance tests are conducted with recombinant ADAMTS13 (b) (4) DP. The specification for (b) (4) DP is a white to off-white colored compact cake. The lot release test for appearance was performed at the Takeda manufacturing (b) (4).

Method

The appearance test for rADAMTS13 (b) (4) lyophilized DP are performed by visual inspection and were assessed as a basic (b) (4) test as per current (b) (4) and performed in accordance with (b) (4).

The reconstituted DP is examined visually under standard conditions and observed for the presence of precipitates and particles.

Method verification

The appearance test for rADAMTS13 (b) (4) DP release is a (b) (4) visual inspection and does not require validation. The batch records indicate that (b) (4) batches of (b) (4) met the specification, and (b) (4) batches of DP 500 IU/Vial and (b) (4) batches of DP 1500 IU/Vial met the specification, verifying the suitability of the method for determining appearance.

Conclusion

The appearance test method is suitable for rADAMTS13 (b) (4) DP release testing at Takeda (b) (4).

2. pH ((b) (4) DP)

Introduction

pH testing is conducted on ADAMTS13 (b) (4) DP at Takeda (b) (4). The specification for (b) (4) DP is 7.0 (b) (4).

Method

The (b) (4) pH test for rADAMTS13 (b) (4) DP is performed according to (b) (4). The lyophilized DP sample is (b) (4).

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7. Reconstitution time (DP)

Introduction

Reconstitution time of lyophilized DP was performed at Takeda (b) (4). The specification (b) (4).

Method

Sterile water for injection (SWFI) is brought to (b) (4) and transferred to the DP vial using the BAXJECT II HI-Flow device. Reconstitution time is measured in (b) (4). The sample is considered resuspended as soon as it has a homogeneous consistency and no undissolved traces can be observed under (b) (4).

Method verification

The lyophilized DP is reconstituted in SWFI within the specification limit ((b) (4)). The test is a simple visual determination and does not require validation or verification ((b) (4)). The reconstitution time for (b) (4) PPQ lots were all (b) (4), confirming the suitability of the test and the specification.

Conclusion

The reconstitution test was appropriately justified for its intended purpose and is suitable for release testing of DP at Takeda (b) (4).

8. Particulate matter (DP)

Introduction

The test for (b) (4) particles is conducted with ADAMTS13 lyophilized DP at a contract laboratory ((b) (4)) located in (b) (4). The specification for (b) (4) is (b) (4).

Method

(b) (4) testing is performed in accordance with (b) (4).

Method Verification

The method was verified for testing the final DP (1500 IU/vial and 500 IU/vial) in accordance with the (b) (4) by examining the following characteristics: Accuracy, repeatability, limit of detection and range. Validation study results were reported in Doc ID-000424939V1.0.

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Conclusion

The method for determination of particulate matter in ADAMTS13 DP is (b) (4) ; the validation data demonstrate the suitability of the method at the stated specification levels.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

10. Residual moisture (DP)

Introduction

Residual moisture content of the DP is measured at Takeda manufacturing (b) (4) ; its release specification is (b) (4).

Method

Residual moisture content of the DP is determined (b) (4) using the (b) (4) Method in accordance with (b) (4) as described in Doc000424888V3.0. The determination of residual moisture is carried out

(b) (4)

Sufficient information has been provided to describe the method.

The system suitability criteria include: (b) (4)

Method Validation

This method was validated as a quantitative assay in Doc000424941V1.0 using the following characteristics: accuracy, precision (repeatability and intermediate precision), specificity, system suitability, limit of detection (LOD), limit of quantitation (LOQ), linearity, range, and robustness.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Conclusion

The analytical procedure for the determination of residual moisture in the DP met the acceptance criteria established in the validation protocol and is suitable for its intended purpose.

11. Polysorbate 80 content (DP)

Introduction

Polysorbate 80 (PS80) is a surfactant that prevents formation of aggregates during lyophilization of the DP; its release specification is (b) (4). The lot release test for quantitation of Polysorbate 80 is performed at the Takeda (b) (4).

Method

The assay procedure for the determination of PS80 content in DP was determined by a spectrophometric method described in Doc 000424906V1.0. (b) (4)

(b) (4)

Sufficient information has been provided to describe the method. The results are valid (b) (4)

(b) (4)

Method Validation

The method was validated as a quantitative assay according to ICH Q2(R1), with results reported in Doc 000424943V1.0. The following validation characteristics were evaluated: (accuracy, precision (repeatability, and intermediate precision), specificity, limit of detection, limit of quantitation, linearity, range, and robustness.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

Conclusion

The analytical procedure for the determination of PS80 in DP met the acceptance criteria established in the validation protocol and is suitable for its intended purpose.

12. Quantitation of Sodium and Calcium (DP)

Introduction

Sodium (Na) and calcium (Ca) are excipients in the DP with a specification of (b) (4) and (b) (4), respectively. The lot release test for quantitation of Na and Ca is performed at Takeda (b) (4).

Method

The quantitative determination of Na and Ca content in lyophilized and aqueous DP samples is performed according to the Doc000424908V1.0 and Doc000424909V1.0 respectively by means of (b) (4)

Sufficient information has been provided to describe the method.

Method Validation

(b) (4)

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Conclusion: The analytical procedure (b) (4) for the determination of sodium and calcium in DP met the acceptance criteria established in the validation protocol and is suitable for its intended purpose.

13. Quantitation of Histidine (DP)

Introduction

The lot release test for quantitation of histidine in the DP is performed at Takeda (b) (4); the specification is (b) (4).

Method

The assay procedure for histidine content determination in DP is described in Doc000424910V1.0. The assay uses (b) (4)

(b) (4)

Sufficient information describing the method has been provided.

The system and sample suitability criteria include:

(b) (4)

(b) (4)

Method validation

The (b) (4) Assay validation was performed according to the validation protocol Doc000424946V1.0 with the following parameters: accuracy, repeatability, intermediate precision, specificity, linearity, range, and robustness.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Conclusion

The analytical procedure for the determination of Histidine in DP by (b) (4) met the acceptance criteria established in the validation protocol and is suitable for its intended purpose.

14 Quantitation of Sucrose (DP)

Introduction

Sucrose is an ingredient of the DP (b) (4) with a specification of (b) (4). Lot release testing performed at Takeda (b) (4).

Method

The (b) (4) Assay for sucrose content in DP is performed according to the Doc000424911V1.0 following ICH Q2 (R1) using (b) (4)

[Redacted]

(b) (4)

Method validation

The validation was performed according to validation protocol Doc 000424947,V 1.0. summarizes the results of accuracy, precision (repeatability and intermediate precision), specificity, quantitation limit, linearity, range, and robustness studies.

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Conclusion

The analytical procedure for the determination of sucrose in DP met the acceptance criteria established in the validation protocol and is validated as a release test for DP.

15. Quantitation of Mannitol (DP)

Introduction

The lot release test for quantitation of Mannitol in DP is performed at the Takeda (b) (4) [Redacted]; Mannitol has a specification of (b) (4) [Redacted].

Method

Mannitol content of DP is determined by (b) (4) [Redacted] according to Doc000424912V1.0. The method is performed in accordance with (b) (4) [Redacted].

Sufficient information on the method has been provided.

The system suitability criteria include (b) (4) [Redacted]

[Redacted]

Method validation

The validation study was executed according to the ICH guidelines following the protocol Doc000424948V1.0 which evaluated accuracy, precision (repeatability and intermediate precision), specificity, linearity, range, and robustness.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Conclusion

The analytical procedure for the determination of Mannitol in DP has met the acceptance criteria and is validated as a release test for this DP.

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(b) (4)

(b) (4)

(b) (4)

(b) (4)

18. Endotoxin ((b) (4) DP)

Introduction

Endotoxin testing for ADZYNMA^{(b) (4)} is performed at Takeda in (b) (4), while DP testing is performed at Takeda in (b) (4). Specification of (b) (4) for (b) (4) DP must be met for release of ADZYNMA.

Methods

The (b) (4) bacterial endotoxin test^{(b) (4)}-BET is performed to quantitate bacterial endotoxins by (b) (4)

(b) (4)

(b) (4)

The method is described in more detail below together with the tests performed to determine the suitability of the test method for its intended use.

The (b) (4) bacterial endotoxin test (b) (4)-BET is a (b) (4)

The method is described in more detail below together with the tests performed to determine the suitability of the test method for its intended use. The original qualification report for the endotoxin study did not include information required for completion of the review. Therefore, an IR was sent requesting missing information and a response was received on July 7, 2023 (Amendment #26) which was found acceptable and explained below.

(b) (4)

(b) (4)-BET Qualification for DP

(b) (4)

The BET concentration results for all (b) (4) DP samples found during the (b) (4) testing were all within the release specification of (b) (4) for ADZYNMA (b) (4) DP and were found acceptable.

Conclusion

The method suitability test was performed and compliant with (b) (4) and the test results indicate there is no product interference from (b) (4) DP test samples, thus indicating the (b) (4) BET test methods are appropriate under the actual conditions of use.

19. Sterility (DP)

Introduction

Sterility testing is performed on the DP at Takeda's manufacturing facility in (b) (4). Acceptance criteria of 'No Growth Detected' must be met for ADZYNMA.

Method

The (b) (4) sterility test is used in accordance with (b) (4). Test samples are (b) (4)

The method is described in more detail below together with the tests that were performed to determine suitability of the test method.

The original submission did not include sterility qualification study; therefore, an IR was submitted to Takeda requesting the study report. A response was received on April 14, 2023 (Amendment #3). Upon review of the response, a follow up IR was submitted requesting additional information be provided. The response was received on September 29, 2023 (Amendment #45), which was found acceptable and explained below.

Sterility Test Qualification for DP

(b) (4)

(b) (4)

(b) (4)

After not more than (b) (4) of incubation, all bacterial and fungal test media had (b) (4) comparable to their respective PC. All NC samples were negative for growth. Positive control (b) (4) confirmed the inoculated microorganism counts were (b) (4) for each challenge microorganism, growth recovered was morphologically indicative of the challenge microorganism.

Conclusion

The method suitability tests were performed and compliant with (b) (4) and the test results indicate there is no product inhibition of microorganism growth, thus indicating the (b) (4) sterility test method is appropriate under the actual conditions of use.

20. Identity of (b) (4) DP

Introduction

The identity of (b) (4) DP is determined by (b) (4), one of two methods to detect rADAMTS13 proteins; the other method is a (b) (4) assay and was reviewed by the Product Office. This identity by (b) (4) is a release and stability test with a specification of (b) (4). The specification for DP is (b) (4) for 500 IU/vial and (b) (4) for 1500 IU/vial. This test is performed at Takeda Manufacturing (b) (4) for (b) (4) DP release testing.

Method

SOP OR1300416 CTP00.05 contains instructions for the identification of rADAMTS13 proteins in (b) (4) DP by (b) (4). An information request was submitted to Takeda requesting the SOP, which was provided in Amendment 43 received on September 18, 2023. This identity assay is a (b) (4). Briefly, (b) (4)

(b) (4)

The validity criteria of the assay include: 1) the result of the rADAMTS13 positive control is within the defined target range, 2) the RSD of the control preparation must be (b) (4), 3) the (b) (4) value of the (b) (4) control must be (b) (4).

Acceptance criteria for samples: 1) the RSD of the sample must be (b) (4), 2) at least (b) (4) of the (b) (4) samples (b) (4) must be within the assay range, 3) the RSD of the individual results of a multiple measurement must be (b) (4).

Method Validation

The sponsor provided validation report 000424607 v1.0 with data supporting the validation of the identity assay by (b) (4) for (b) (4) DP. Assay specificity, accuracy, precision, limit of quantitation, linearity, range, and robustness were evaluated.

(b) (4)

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Conclusion

The (b) (4) to determine identity of rADAMST13 proteins in (b) (4) DP was well described and validation data show the method performed at Takeda (b) (4) site is suitable for release testing.

(b) (4)

[Redacted]

[Redacted]

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