

DBSQ/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125810/0

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Product: YIMMUGO, Immune Globulin Intravenous (Human)

Applicant: Biotest AG

Subject: Analytical Methods used for the Lot release of YIMMUGO (b) (4)
Drug Product (DP).

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of YIMMUGO (b) (4) DP, including the associated method validations, were reviewed:

1. (b) (4) methods for:
 - a. Appearance (clarity/opalescence) of DP by (b) (4) (Emnet Yitbarek)
 - b. Appearance (coloration) of DP by (b) (4) (Emnet Yitbarek)
 - c. Appearance (visible particulates) of DP by visual inspection (Emnet Yitbarek)
 - d. Extractable Volume of DP by (b) (4) (Emnet Yitbarek)
 - e. pH of (b) (4) DP by (b) (4) (Emnet Yitbarek)
 - f. Osmolality of DP by (b) (4) (Emnet Yitbarek)
2. Total protein concentration of (b) (4) DP by (b) (4) (Emnet Yitbarek)
3. (b) (4) DP by (b) (4)
(b) (4) (Emnet Yitbarek)
4. Glycine concentration in DP by (b) (4)
(b) (4) (Emnet Yitbarek)
5. Polysorbate 80 (PS80) concentration in DP by (b) (4) (Emnet Yitbarek)

Documents Reviewed

Information in sections 2.2, 2.3, (b) (4) (b) (4) 3.2.P.1, (b) (4) 3.2.P.6, and 3.2.R of the original submission describing (b) (4) DP characteristics, specifications, analytical procedures and validation reports were reviewed.

Background

On August 29, 2023, Biotest AG submitted a BLA, STN 125810, for YIMMUGO (BT595), a 10% polyclonal human Immune Globulin Intravenous (IgIV) liquid, for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age or older. The active ingredient is human immunoglobulin (Ig) purified from source human plasma and contains 100±10 mg/ml protein, with at least 96% IgG and a maximum of (b) (4) IgA and (b) (4) IgM. DP (b) (4) solutions with slightly opalescent and pale-yellow clarity/coloring and the DP (YIMMUGO) is supplied in 5g/50ml, 10g/100ml and 20g/200ml single-dose vials. Human IgG is a protein with a (b) (4) (b) (4)

The final container DP is formulated with (b) (4) glycine and (b) (4) polysorbate 80 in water for injection (WFI) at pH (b) (4)

This memo includes the review of all physicochemical methods listed in the summary section above that are used for release testing of YIMMUGO (b) (4) DP and their validation/verification. The site responsible for the manufacture, release testing and validation of (b) (4) DP analytical methods is Biotest AG located at Landsteinerstraße. 5 63303 Dreieich, Germany.

1. (b) (4) methods:

a. Appearance (clarity/opalescence) of DP

The degree of opalescence/clarity (appearance) of the samples is measured by (b) (4)

hence the criteria were met and Biotest Dreieich is qualified to perform clarity/opalescence release testing on DP samples.

b. Appearance (coloration) of DP

Coloration testing of DP is a qualitative test performed in accordance with (b) (4)

(b) (4) The test is performed following an (b) (4) method SOP-Q-00311. The release specification requires DP must be (b) (4) The method was verified using batch records of (b) (4) DP lots which met the release criteria; hence, Biotest Dreieich is qualified to perform coloration release testing on DP samples.

c. Appearance (visible particulates) of DP

Visible particle testing for DP is a qualitative test performed in accordance with (b) (4)

(b) (4) by visual inspection. (b) (4) against a (b) (4) The test is performed following an (b) (4) method SOP-Q-00262. The DP release specification requires DP samples to be essentially free from visible particulates. The method was verified using batch records of (b) (4) DP lots which met the release criteria; hence, Biotest Dreieich is qualified to perform visible particulates release testing on DP samples.

d. Extractable volume of DP

Extractable volume for DP is a quantitative test performed in accordance with (b) (4) (b) (4) and used to (b) (4)

The test is performed following an internal test method SOP-Q-00197. The DP release specification requires volume must be \geq nominal (label) volume; YIMMUGO is supplied in 50ml, 100ml and 200ml single-dose vials. The method was verified using batch records of (b) (4) DP lots of (b) (4) dose, which met the release criteria; hence, Biotest Dreieich is qualified to perform extractable volume release testing on DP samples.

e. pH of (b) (4) DP

pH is a quantitative test performed in accordance with (b) (4) DP using a (b) (4) The test is performed following an internal test method SOP-Q-00050. The release specification requires pH of (b) (4) DP to be within 4.4-5.2. The method was verified fo (b) (4)

hence, the criteria were met and Biotest Dreieich is qualified to perform pH release testing on (b) (4) DP samples.

f. Osmolality of DP

Osmolality is a quantitative test performed in accordance with (b) (4) by (b) (4) The test is performed following an (b) (4) method SOP-Q-00336. The release specification for DP osmolality is 280-380 mOsm/kg. The method was verified for (b) (4)

The results show (b) (4) (b) (4) hence the criteria were met and Biotest Dreieich is qualified to perform osmolality release testing on DP samples.

2. Total protein concentration of (b) (4) DP

Introduction

The purpose of this quantitative analytical procedure is to quantify the total protein concentration of YIMMUGO (b) (4) DP samples by (b) (4) method using (b) (4) The test is performed following an internal test method SOP-Q-00593, which is based on (b) (4) (b) (4) standard protocols. The method is based on the (b) (4) (b) (4)

The total protein release specifications for (b) (4) DP are (b) (4) and (b) (4) respectively.

Method

Total protein concentration of (b) (4) DP is measured (b) (4)

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

(b) (4)

4. Quantitation of Polysorbate 80 in (b) (4) DP samples by (b) (4)

Introduction

The purpose of this analytical procedure (SOP-Q-00440) is to quantify Polysorbate 80 (PS80) concentration in (b) (4) DP samples by (b) (4)

(b) (4) The method is performed according to (b) (4)

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(b) (4)

Conclusion

PS80 quantitation by (b) (4) (SOP-Q-00440) was appropriately validated for its intended purpose at Biotest Dreieich QC Lab and is suitable for the determination of PS80 concentration in (b) (4) DP samples.

5. Determination of glycine in (b) (4) DP by (b) (4)

Introduction

The purpose of this analytical procedure (SOP-Q-00168) is to quantify glycine concentration in (b) (4) DP samples by (b) (4) with an

(b) (4)

The method is based on (b) (4)

(b) (4)

Glycine is an excipient in YIMMUGO

(b) (4) DP and serves as a stabilizing agent. (b) (4)

The final (DP) formulation contains (b) (4) glycine and the release specification for (b) (4) DP are (b) (4) and (270-330 mM) respectively.

Method

(b) (4)

(4)

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

(b) (4)

Conclusion

Glycine quantitation by (b) (4) (SOP-Q-00168) was appropriately validated for its intended purpose at Biotest Dreieich QC Lab and is suitable for the determination of glycine in (b) (4) DP samples.