

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761140Orig1s000

PRODUCT QUALITY REVIEW(S)



**U.S. FOOD & DRUG
ADMINISTRATION**

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	12/16/2020
Assessor:	Scott Dallas and Jim Barlow, RPh, Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Kristen Nickens, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761140
Applicant:	Amgen, Inc.
Submission Date:	December 19, 2019; July 23, 2020; August 20, 2020; November 3, 2020; December 4, 2020; December 11, 2020; December 15, 2020 and December 1, 2020.
Product:	Riabni (rituximab-arxx)
Dosage form:	Injection
Strength and Container-Closure:	100 mg/10 mL (10 mg/mL) and 500 mg/50 mL (10 mg/mL) solution in single dose vials
Purpose of assessment:	The Applicant submitted a biologics license application seeking approval as a biosimilar to the reference product Rituxan (rituximab) BLA 103705. The proposed indications and dosing are based on those approved for rituximab, subject to exclusivities that may be in effect at the time of submission.
Recommendations:	The prescribing information, medication guide, container labels and carton labeling are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

The applicant has proposed to use two sites for their packaging and labeling operations. The two sites are Amgen Europe B.V. (Referred to as ABR) and Amgen Manufacturing Ltd. (referred to as AML). The applicant has submitted a slightly different layout for the container and carton labeling for each strength for both sites. Refer to Appendix A & C.

CONCLUSION

The prescribing information and the medication guide were submitted on December 15, 2020. The carton labeling packaged at Amgen Manufacturing Ltd (Referred to as AML) along with the carton labeling packaged at Amgen Europe B.V. (Referred to as ABR) were submitted on December 11, 2020. The container label for the 100 mg/10 mL strength vials (ABR container) was submitted on December 15, 2020; The container labels for the 500 mg/50 mL strength vials for both the ABR container and the AML container were submitted on December 17, 2020 and the container label for the 100 mg/10 mL strength vial (AML container) was submitted on December 11, 2020 and were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on December 19, 2019)
<\\cdsesub1\evsprod\bla761140\0001\m1\us\draft-labeling-text-uspi.docx>
- Medication Guide (submitted on December 19, 2019)
<\\cdsesub1\evsprod\bla761140\0001\m1\us\draft-labeling-text-medguide.docx>
- Container Labels (submitted on December 19, 2019)
Drug product packaging and labeling:
Site a: Amgen Europe B.V. (Referred to as ABR)
Site b: Amgen Manufacturing Ltd. (referred to as AML)



Appendix B: Evaluation Tables**Evaluation Tables:** Label^{1,2} and Labeling³ Standards**Container⁴ Label Evaluation**

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form below the proper name)</i>	☒ Yes ☐ No ☐ N/A

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as “final container”) is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A

Lot number or other lot identification (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ N/A

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

This regulation does not apply, because this product is supplied as a single-dose container.

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A

⁵ Per 21 CFR 610.60 (c) *Partial label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

<i>Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
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Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: This regulation does not apply, because this product is supplied as a single-dose container.
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Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The container label is too small to include a Medication Guide statement, which is acceptable.
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No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: This product has a carton, so this regulation does not apply.

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☒ Yes ☐ No ☐ N/A

Ferrule and cap overseal (for vials only)	Acceptable
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<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A
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Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A

Route of administration (container label)	Acceptable
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

NDC numbers (container label)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Preparation instructions (container label)	Acceptable
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
<i>Preparation instructions are not needed for this product, so this regulation does not apply.</i>

Package type term (container label)	Acceptable
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Misleading statements (container label)	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No

	☒ N/A
Prominence of required label statements (container label)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A
Spanish-language (Drugs) (container label)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

The label is considered a partial label per 21 CFR 610.60 (c). Thus, the applicant will not be requested to add an inactive ingredient statement.

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☒ Yes ☐ No ☐ N/A

Package⁶ Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	Acceptable
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⁶ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	☒ Yes ☐ No ☐ N/A

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
This regulation does not apply, because this product is supplied as a single-dose container.

Preservative (package labeling)	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:
The labeling contains a "No preservative" statement.

Number of containers (package labeling)	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A

Product Strength (package labeling)	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize</i>	☒ Yes ☐ No

<i>Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters: <7> Labeling</i>	☐ N/A
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<u>Storage temperature/requirements (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

<u>Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

<u>Multiple dose containers (recommended individual dose) (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: This regulation does not apply, because this product is supplied as a single-dose container.
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<u>Route of administration (package labeling)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

<u>Known sensitizing substances (package labeling)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The carton does not contain any statements because there are no known sensitizing substances.

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Source of the product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

The source of the product is not a safety factor and thus is not noted on the carton labeling.

Minimum potency of product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

The carton displays a "No U.S. standard of potency" statement.

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

A distributor is not listed on the carton labeling.

Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

This product is not seeking exceptions to labeling per 21 CFR 610.68.

NDC numbers (package labeling)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: <i>Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

This carton labeling does not need to include preparation instructions.

Package type term (package labeling)	Acceptable
Recommended labeling practices: <i>Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Misleading statements (package labeling)	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
There are no misleading statements.

Prominence of required label statements (package labeling)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i>	☒ Yes ☐ No ☐ N/A

<i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	
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Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☒ Yes ☐ No ☐ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The label displays an acceptable Medication Guide statement.
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Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☒ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	Acceptable

Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
<u>2 DOSAGE AND ADMINISTRATION</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(3)(iv)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
<u>3 DOSAGE FORMS AND STRENGTHS</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
<u>11 DESCRIPTION</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: the pH adjuster has been added per request. ACCEPTABLE

Full Prescribing Information	
15 Cytotoxic Drug reference	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv) xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures.1 1.OSHA Hazardous Drugs. OSHA. [Accessed on June 9, 2017, from http://www.osha.gov/SLTC/hazardousdrugs/index.html	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	Acceptable
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to include the proper name in the title block.

MEDICATION GUIDE	
STORAGE AND HANDLING	Acceptable
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The medication guide does not contain a storage and handling section.

MEDICATION GUIDE	
INGREDIENTS	Acceptable
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
MANUFACTURER INFORMATION	Acceptable
21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
<i>21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on December 15, 2020)
<\\CDSESUB1\evsprod\bla761140\0030\m1\us\s-riabni-us-pi-v1-original-application-c-2020-1214.pdf>
- Medication Guide (submitted on December 15, 2020)
<\\CDSESUB1\evsprod\bla761140\0030\m1\us\s-riabni-us-mg-v1-original-application-c-2020-1214.pdf>
- **Carton Labels**
The applicant has proposed to use two sites for their packaging and labeling operations. The two sites are Amgen Europe B.V. (Referred to as ABR) and Amgen Manufacturing Ltd. (Referred to as AML). The applicant has submitted a slightly different layout for the container and carton labeling for each strength for both sites.

500 mg/50 mL (10 mg/mL) – AML (Carton) submitted on 12/11/2020

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



James
Barlow

Digitally signed by James Barlow

Date: 12/16/2020 04:25:30PM

GUID: 508da70800028bcca2d0465dabab258f

Comments: Here is the follow-up to be signed Kristen. THank you



Kristen
Nickens

Digitally signed by Kristen Nickens

Date: 12/16/2020 04:28:19PM

GUID: 54b821c400083afe9702573df3fd56c4

First Approval for Indication/First Biosimilar/Expedited or Breakthrough Assessment: No

Recommendation: Approval

BLA Number: 761140
Assessment Number: 1
Assessment Date: 10/16/2020

Drug Name/Dosage Form	Riabni (rituximab-arrrx), Injection
Strength/Potency	100 mg/10 mL, 500 mg/50 mL
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indication	All indications approved for US-licensed Rituxan: Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis) and microscopic polyangiitis
Applicant/Sponsor	Amgen, Inc.
US agent, if applicable	N/A

Product Overview:

Riabni (rituximab-arrrx, ABP 798) is a chimeric monoclonal IgG1 antibody developed as a biosimilar to US-licensed Rituxan (rituximab). Rituximab-arrrx binds to the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes, as well as malignant B cells. Upon binding to CD20, rituximab-arrrx mediates B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and apoptosis, which are particularly applicable to the mechanisms of action of rituximab-arrrx in B cell malignancies and autoimmune diseases.

The rituximab-arrrx molecule is constructed as a chimera of mouse variable regions that bind human CD20 on a human IgG1 backbone. The molecule has one N-linked glycosylation site on each heavy chain, important in eliciting the Fc effector functions relevant to the mechanisms of action.

Rituximab-arrrx is produced in genetically engineered Chinese Hamster Ovary (CHO) cells. Rituximab-arrrx drug product, Riabni, is manufactured to have the same strengths, dosage form, and route of administration as US-licensed Rituxan. Riabni also has the same formulation and presentations as US-licensed Rituxan. Riabni is a sterile, preservative-free colorless to pale yellow, clear to opalescent solution for intravenous infusion, supplied in single-dose vials containing rituximab-arrrx at 100 mg/10 mL or 500 mg/50 mL.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance/Drug Product/Immunogenicity	Amy Hsu	OPQ/OBP/DBRR1
Comparative Analytical Assessment	Amy Hsu	OPQ/OBP/DBRR1
Labeling	James Barlow/Vicky Borders-Hemphill	OPQ/OBP
Drug Substance Microbiology/DS Facility	Zhong Li/Maxwell Van Tassell (TL)/Thuy T. Nguyen (BC)	OPMA/DBM/BMB1
Drug Product Microbiology/DP Facility	Amy Devlin/Maxwell Van Tassell (TL)/Thuy T. Nguyen (BC)	OPMA/DBM/BMB1
RBPM	Anh-Thy Ly	OPQ/OPRO/DRBPMI/RBPMB1

Application Team Lead	Kristen Nickens	OPQ/OBP/DBRR1
Review Chief	Qing Zhou	OPQ/OBP/DBRR1

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Beatrice Kallungal/Theresa Carioti (TL)	OND/ORO/DROOD
Cross-disciplinary Team Lead	Nicholas Richardson	OND/OOD/DHMII
Clinical/Medical Officer	Pam Seam/Nicholas Richardson (TL)	OND/OOD/DHMII
	Juwaria Waheed/Anil Rajpal (TL)	OND/OII/DRTM
Pharmacology/Toxicology	Simon Williams/Brenda Gehrke (TL)	OND/OOD/DHOT
Clinical Pharmacology	Shalini Wickramaratne/Senarath Yapa/Ping Ji (TL)/Salaheldin Hamed (TL)	OTS/OCP/DIIP
Statistics	Laura Fernandes/Yute Wu (TL)	OTS/OB/DBIX
	William Koh/Rebecca Rothwell (TL)/Yongman Kim (TL)	OTS/OB/DBII
	Yu-Ting Weng/Meiyu Shen (TL)	OTS/OB/DBVI

1. Names:

- a. Proprietary Name: Riabni
- c. Non-Proprietary Name/USAN: rituximab-arrx/rituximab
- d. CAS Name: 1446410-99-6
- e. Common Name: ABP 798
- f. INN Name: N/A
- g. Compendial Name: N/A
- h. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P11836 (CD20_HUMAN) [ABP 798]

Submissions Assessed:

Submission(s) Assessed	Document Date
761140/001	12/19/2019
761140/004 (Information Request #1 - OPMA)	2/4/2020
761140/007 (Information Request #2 - OPMA)	4/24/2020
761140/008 (Information Request #3 – OBP comparative analytical data)	5/8/2020
761140/009 (Information Request #4 – OBP comparative analytical data)	5/27/2020
761140/0010 (Information Request #5 – OPMA and OBP)	6/17/2020
761140/0011 (Information Request #6 - OBP)	6/29/2020
761140/0012 (Information Request #7 - OBP)	7/21/2020
761140/0015 (Information Request #8 – OPMA and OBP)	8/11/2020
761140/0017 (Information Request #9 – OBP)	8/13/2020
761140/0024 (Information Request #10, #6, #9 – OBP)	9/30/2020
761140/0025 (Information Request #11 – OBP)	10/15/2020
761140/0026 (Information Request #12 – OBP)	10/29/2020

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(k)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Assessment Completed
(b) (4)	3	(b) (4)	Glass vials	3	Adequate	N/A
	3		Stopper	3	Adequate	N/A
	5	(b) (4)		2	Adequate	N/A

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows:
2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed).

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	118281	Amgen-sponsored IND under which ABP 798 was developed and BPD meetings were held

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion: Amgen claimed a categorical exclusion from the preparation of an environmental assessment for Riabni in accordance with 21 CFR 25.31(c). The claim states that Riabni is considered "naturally occurring in the environment," therefore, exposure to the environment is not expected to significantly alter the concentration of the substance, its metabolites, or degradation products in the environment. The claim of a categorical exclusion is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761140 for Riabni manufactured by Amgen, Inc. The data submitted in this application are adequate to support the conclusion that:

- The manufacture of Riabni is well-controlled and leads to a product that is pure and potent;
- The comparative analytical data supports a demonstration that rituximab-arxx is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components.

It is recommended that this product be approved for human use under the conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
 - o Drug Substance: Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI), 40 Technology Way, West Greenwich, Rhode Island 02817, FEI: 3003359885
 - o Drug Product: [REDACTED] (b) (4)
- Fill size and dosage form: 100 mg/10 mL single-use vial, 500 mg/50 mL single-use vial
- Dating period:
 - o Drug Product: 36 months at 2 to 8°C
 - o Drug Substance: (b) (4) months at (b) (4) °C
 - o For packaged products: "Not packaged"
- Exempt from lot release:
 - o Yes
 - o Rationale, if exempted: Riabni is exempted from lot release per FR 95-29960 considering that well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products are exempt from 21 CFR 601.2a lot release requirements.

C. Benefit/Risk Considerations:

Riabni (rituximab-arxx, ABP 798) is a proposed biosimilar to US-licensed Rituxan and proposed for use in all eligible indications approved for US-licensed Rituxan (Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis) and microscopic polyangiitis).

To support a demonstration that Riabni is highly similar to US-licensed Rituxan and to establish the analytical component of the scientific bridge to support the relevance of the data generated from studies using EU-approved MabThera as the comparator to the assessment of biosimilarity, Amgen performed a three pairwise comparative analytical assessment of ABP 798, US-licensed Rituxan, and EU-approved MabThera.

As part of the comparative analytical assessment, the molecular attributes of rituximab were collectively assigned to appropriate statistical assessment categories and a sufficient number of lots of each of the three products were evaluated. A comprehensive array of analytical methods, demonstrated as suitable to evaluate the critical quality attributes of rituximab-arrx and US-licensed Rituxan, were used to support the demonstration that the products are highly similar. The same analytical methods and statistical approaches were used to support establishment of the analytical portion of the scientific bridge. The comparative analytical assessment data provided support the conclusion that Riabni is highly similar to US-licensed Rituxan, and that the analytical portion of the scientific bridge was established.

The OPQ review of the manufacturing and controls has identified that the methodologies and processes used for drug substance (DS) and drug product (DP) manufacturing, release and stability testing are sufficient to assure a consistent and safe product.

The commercial manufacture of rituximab-arrx DS at Immunex Rhode Island (ARI) is recommended for approval by Office of Pharmaceutical Manufacturing Assessment (OPMA) through the review of requested manufacturing site records in lieu of an on-site inspection under Section 704(a)(4) (FDASIA Sec. 706). A pre-license inspection for the manufacture of Riabni DP at (b) (4) was recommended to be waived by OPMA based on the firm's compliance history, current acceptable cGMP status, and the aseptic manufacture of other licensed products on the same vial-filling line.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:
None.

II. Comparative Analytical Assessment and Evaluation of the Analytical Component of the Scientific Bridge

I. Analytical Assessment Overview and Conclusions

Amgen performed a comparative analytical assessment using 37 lots of US-licensed Rituxan (US-Rituxan) (21 lots of 100 mg; 16 lots of 500 mg), 30 lots of EU-approved rituximab (EU-MabThera) (15 lots of 100 mg; 15 lots of 500 mg), and 14 independent lots of ABP 798 drug product (DP) (13 lots of 100 mg; 1 lot of 500 mg). The ABP 798 lots evaluated included development, nonclinical, clinical, and process validation lots. ABP 798 clinical lots (manufactured over the course of development) used in both the comparative clinical study 20130109 in patients with CD20 positive B cell non-Hodgkin's lymphoma and the PK similarity and comparative clinical study 20130108 in patients with rheumatoid arthritis, were included in the comparative analytical assessment. The comparative analytical assessment also included US-Rituxan and EU-MabThera lots used in these clinical studies. For the analysis of attributes impacted by the DP manufacturing process, a total of

26 ABP 798 DP lots were evaluated (14 lots of 100 mg and 12 lots of 500 mg). The analytical assessment included:

- Extensive comparative physiochemical and functional assessments of quality attributes.
- Comparative assessments of the degradation profiles under forced degradation conditions.

Amgen used a risk-based approach for statistical evaluation of the analytical results:

- High risk-ranked attributes tested using quantitative assays were evaluated by equivalence testing.
- Moderate risk-ranked attributes tested using quantitative assays were evaluated by quality ranges (QR) (non-adjusted, age-adjusted or initial time point quality ranges) or using an expectation approach in which individual values were compared to a pre-defined limit or interval based on method capability and product knowledge. Age-adjusted quality ranges were considered as supportive data as part of the comparative analytical assessment.
- Low risk-ranked attributes or attributes tested using qualitative assays were evaluated using side-by-side visual comparisons.

Results from method validation, qualification, verification and transfer studies were provided to support the suitability of the methods used in the comparative analytical assessment.

Based on our assessment of the ABP 798 and US-Rituxan data, the data support a demonstration that ABP 798 is highly similar to US-Rituxan, notwithstanding minor differences in clinically inactive components. ABP 798 has the same strengths, dosage form, and route of administration as US-Rituxan. ABP 798 has the same formulation and presentation as US-Rituxan. Amgen used a comprehensive array of analytical methods that were suitable to evaluate the critical quality attributes of ABP 798 and US-Rituxan to support the demonstration that the products are highly similar. The numbers and types (strengths, expiry range, purpose of material) of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the analytical studies. The observed differences do not preclude a demonstration that ABP 798 and US-Rituxan are highly similar.

In addition, three pairwise comparisons of ABP 798, US-Rituxan, and EU-MabThera were used to establish the analytical component of the scientific bridge to support the relevance of the data generated from studies using EU-MabThera as the comparator to the assessment of biosimilarity. Amgen supported the establishment of the analytical portion of the scientific bridge using the same methods and statistical approaches used to support a demonstration that ABP 798 is highly similar to US-Rituxan. Based on our review of the data, we conclude that the analytical portion of the scientific bridge was established.

II. Comparative Analytical Assessment Results

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary Structure	Amino acid sequence	Yes	Yes

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
	Molecular weight (intact, reduced, and deglycosylated heavy chain and light chain)	Yes	Yes
	Disulfide structure	Yes	Yes
	Glycan mapping	Yes	Yes
	Extinction coefficient	Yes	Yes
	Isoelectric point	Yes	Yes
	Identity by anti-idiotypic ELISA	Yes	Yes
Glycosylation	Afucosylation (alone and total)	Yes	Yes
	High mannose	Yes	Yes
	Galactosylation	Yes	Yes
	Sialylation	Yes	Yes
Post Translational Modifications	Oxidation	Yes	Yes
	Deamidation	Yes	Yes
	Glycation	Yes	Yes
	C-terminal lysine	Yes	Yes
	N-terminal pyroglutamic acid	Yes	Yes
Bioactivity	Complement-dependent cytotoxicity (CDC)	Yes	Yes
	Antibody-dependent cellular cytotoxicity (ADCC)	Yes	Yes
	Antibody-dependent cellular phagocytosis (ADCP)	Yes	Yes
	CD20 binding	Yes	Yes
	Apoptosis	Yes	Yes
	FcγRIIIa (158V/F) receptor binding	Yes	Yes
	C1q binding	Yes	Yes
	Binding to other Fcγ receptors (FcγR1a, FcγRIIa, FcγRIIb, FcγRIIIb)	Yes	Yes
Purity and product related variants or impurities	Size variants-high molecular weight (HMW) species	Yes*	Yes*
	Size variants-molar mass	Yes*	Yes*
	Aggregates	Yes	Yes

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
	Fragmentation and non-glycosylated heavy chain (NGHC)	Yes*	Yes*
	Partially reduced species	Yes*	Yes*
	Charged variants	Yes	Yes*
Higher Order Structure	Secondary structure	Yes	Yes
	Tertiary structure	Yes	Yes
	Thermal stability/melting temperature	Yes	Yes
Drug Product Attributes	Protein content	Yes	Yes
	Deliverable volume	Yes	Yes
	Subvisible particles	Yes*	Yes*

“*”: Differences were noted, but do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge and will be discussed further below.

The comparative assessment of the degradation profiles of ABP 798, US-Rituxan and EU-MabThera under forced degradation conditions, including thermal stress and ultraviolet light exposure show minor differences among the three products attributed to method and experimental variability (studies not performed side-by-side, different stability chambers used and temperature fluctuations). Considering the data and justifications for the minor differences observed, the results do not preclude a demonstration that ABP 798 is highly similar to US-Rituxan or the establishment of the analytical component of the scientific bridge.

III. Analytical Studies to Support the Use of a Non-US-Licensed Comparator Product

The clinical development of ABP 798 included two clinical studies:

- Study 20130108: A randomized, double-blind study to compare pharmacokinetics and pharmacodynamics, efficacy and safety and immunogenicity of ABP 798, US-Rituxan, and EU-MabThera in patients with moderate to severe rheumatoid arthritis
- Study 20130109: A randomized, double-blind study comparative clinical study comparing the efficacy, safety and immunogenicity of ABP 798 and US-Rituxan in patients with CD20 positive B-cell non-Hodgkin’s lymphoma

To support the relevance of the clinical data generated using EU-MabThera as a comparator product in Study 20130109, Amgen performed three, pairwise analytical assessments using a comprehensive array of analytical methods and a three-way PK similarity study (20130108). To support the establishment of the analytical component of the scientific bridge, Amgen included comparisons of ABP 798 to US-Rituxan, ABP 798 to EU-MabThera, and EU-MabThera to US-Rituxan. The same analytical methods used for supporting a demonstration that ABP 798 is highly similar to US-Rituxan were used for the pairwise analytical comparisons with EU-MabThera. The differences observed in the analytical studies do not preclude the establishment of the analytical component of the scientific bridge. See section IV below. The results support the establishment of the analytical component of the scientific bridge.

IV. Assessment of Comparative Analytical Study Results

Comparative analytical acceptance criteria were met for all attributes evaluated with quality ranges with the following exceptions:

1. Size variants-HMW species: Analytical results generated by SE-UHPLC using the non-adjusted quality range approach show two ABP 798 lots (ABP 798 data range HMW species: 0.8-1.5%; monomer: 98.5-99.2%) were slightly above the upper limit of the US-Rituxan quality range (QR: 0.43-1.47%) for HMW species. The same two ABP 798 lots were also slightly above the upper limit of the EU-MabThera quality range for HMW species (QR: 0.46-1.46%). All ABP 798 lots were within the US-Rituxan (QR: 98.42-99.48%) and EU-MabThera (QR: 98.44-99.40%) quality range for % monomer. Additionally, the chromatographic profiles of ABP 798 lots were different with respect to HMW species peak shape and size distribution compared to US-Rituxan and EU-MabThera, with no observed difference in monomer peak shape or distribution between ABP 798 lots, US-Rituxan and EU-MabThera. The results of the SE-UHPLC analysis indicate that there are minor differences in % HMW species in ABP 798 compared to US-Rituxan and EU-MabThera. The residual uncertainty with respect to the differences in HMW species is addressed by the small magnitude ($< 0.1\%$) of the difference in % HMW species detected in the ABP 798 lots above the US-Rituxan QR and EU-MabThera QR. Additionally, characterization of enriched HMW species and molar mass analysis of size variants by SE-HPLC-SLS further addresses the residual uncertainty regarding the differences noted in the HMW species peak shape and size distribution in the ABP 798 lots compared to the US-Rituxan and EU-MabThera lots (see #6 below). Thus, the differences do not preclude a demonstration that ABP 798 is highly similar to US-Rituxan or the establishment of the analytical component of the scientific bridge.
2. NGHC: Analysis by reduced CE-SDS using the non-adjusted quality range analysis showed that all 14 lots of ABP 798 (ABP 798 NGHC data range: 0.5-0.6%) were slightly above the upper limit of the US-Rituxan quality range (QR: 0.29-0.53%) for NGHC and 6 of the 14 ABP 798 lots were slightly above the upper limit of the EU-MabThera quality range (QR: 0.26-0.59%). The results of the reduced CE-SDS assay indicate that there are differences in % NGHC between ABP 798, US-Rituxan and EU-MabThera. The residual uncertainty is addressed by the small magnitude ($< 0.1\%$) of the difference in the amount of % NGHC detected in the ABP 798 lots above the upper limit of the US-Rituxan QR and the EU-MabThera QR. Additionally, while differences in NGHC can impact biological activity, such as complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC), the equivalence testing results confirmed that the differences in NGHC between ABP 798, US-Rituxan, and EU-MabThera did not impact biological activity, including bioactivity as measured by CDC and ADCC. Thus, the differences noted do not preclude a demonstration that ABP 798 is highly similar to US-Rituxan or the establishment of the analytical component of the scientific bridge.
3. Partially reduced species: Analysis by non-reduced CE-SDS using the non-adjusted quality range analysis showed that the main peak (ABP 798 data range: 95.9-98.8%) and pre-peaks (ABP 798 data range: 1.2-4.1%) results for 10 of the 14 ABP 798 lots were outside of the US-Rituxan quality ranges (QR for main peak: 96.34-97.90%; QR for pre-peaks: 2.10-3.65%) and EU-MabThera quality ranges (QR for main peak: 96.48-97.80%; QR for pre-peaks: 2.20-3.52%). The results of the non-reduced CE-SDS assay indicate that there are differences in % main peak and % pre-peak between ABP 798, US-Rituxan, and EU-MabThera. The residual uncertainty is addressed by the small magnitude of the differences ($< 1.0\%$) in both % main peak and % pre-peak of the ABP 798 lots above the US-Rituxan QR and EU-MabThera QR. Additionally, while the differences in partially reduced species can impact biological activity,

such as CDC and ADCC, the characterization data showed no impact on biological activity, as measured by CDC and ADCC, in the presence of up to 47.7% pre-peak. Further, the equivalence testing results confirmed that the differences in partially reduced species between ABP 798, US-Rituxan, and EU-MabThera did not impact biological activity, including bioactivity as measured by CDC and ADCC. Thus, the differences noted do not preclude a demonstration that ABP 798 is highly similar to US-Rituxan or the establishment of the analytical component of the scientific bridge.

4. Charge variants: Analysis by CEX-HPLC using the non-adjusted quality range analysis showed that the % basic species (ABP 798 data range: 7.7-9.2%) of two of the 14 lots of ABP 798 were slightly below the lower limit of the EU-MabThera quality range (QR: 8.07-13.61%). The results of the CEX-HPLC assay indicate that there are minor differences in % basic species between ABP 798 and EU-MabThera. The residual uncertainty is addressed by the small magnitude of the difference (<0.4%) between the % basic species detected in the ABP 798 lots above the upper limit of the EU-MabThera QR. Additionally, while differences in charge variants can impact biological activity, such as CDC and ADCC, the charge variant characterization data demonstrated no difference in CDC and ADCC biological activity in enriched basic species fractions (relative to the unfractionated starting material) between the ABP 798 and EU-MabThera lots evaluated. Further, the equivalence testing results confirmed that the differences in charge variants between ABP 798 and EU-MabThera did not impact biological activity, including bioactivity as measured by CDC and ADCC. Thus, the differences noted in % basic species do not preclude the establishment of the analytical component of the scientific bridge.
5. Subvisible particles: Subvisible particles are not expected to be evaluated as part of the comparative analytical assessment and will be controlled as part of the overall ABP 798 manufacturing process control strategy. Nonetheless, Amgen provided this information as part of their comparative analytical assessment, and for completeness, the comparative data for this attribute was reviewed and discussed. Subvisible particle data analyzed by microflow imaging (MFI) were evaluated using quality ranges. Four of the 26 ABP 798 drug product lots evaluated (ABP 798 data range: 0-508 particles/mL) were above the upper limit of the US-Rituxan quality range for non-spherical particles of ≥ 5 μ m (QR: 0-248 particles/mL), and 6 of the 26 ABP 798 lots were above the upper limit of the EU-MabThera quality range (QR: 0-71 particles/mL). The results of the MFI assay indicate that there are minor differences in ≥ 5 μ m non-spherical particles between ABP 798, US-Rituxan and EU-MabThera. All ABP 798 lots were within the US-Rituxan and EU-MabThera quality ranges for total subvisible particles of ≥ 5 μ m. Moreover, the differences in the non-spherical particles of ≥ 5 μ m detected in the ABP 798 lots above the US-Rituxan QR and the EU-MabThera QR were of a small magnitude and were only observed in a small number of lots.

Comparative analytical criteria were met for all attributes evaluated by qualitative visual assessments with the following exceptions:

6. Size variants-molar mass: Analysis by static light scattering detection (SE-HPLC-SLS) showed different chromatogram profiles with respect to sub-peaks of HMW species identified as HMW_a, HMW_b, HMW_c, in ABP 798, US-Rituxan and EU-MabThera. The chromatograms were consistent with the SE-UHPLC analysis. The molar mass results for the three HMW species peaks identified were shown to be consistent across all nine batches of ABP 798, US-Rituxan, and EU-MabThera evaluated. Further analysis by SE-HPLC-SLS in fractionated and enriched HMW species showed

similar molar masses of the peaks (HMW_a, HMW_b, and HMW_c) collected at similar elution times that contribute to the total HMW species peak. The results of the SE-HPLC-SLS analysis indicate that there are minor differences in HMW species peak distribution between ABP 798, US-Rituxan and EU-MabThera, with no observed difference in the monomer peak among the three products. The residual uncertainty is addressed by the consistent molar masses detected across the different sub-peaks of the HMW species identified at similar elution times. Additionally, while differences in size variants can impact biological activity, such as CDC and ADCC, the results of the additional characterization of the fractionated and enriched size variants showed consistent results in potency, including bioactivity as measured by CDC and ADCC, across the three products. The differences do not preclude a demonstration that ABP 798 is highly similar to US-Rituxan or the establishment of the analytical component of the scientific bridge.

V. Same Strength(s)

ABP 798 has the same dosage form and route of administration as US-Rituxan. Amgen is seeking approval for the 100 mg/10 mL and 500 mg/50 mL strengths in a vial. US-Rituxan is available at these strengths and in this presentation¹. Comparative protein concentration (mg/mL) and deliverable volume, assessed as part of the comparative analytical assessment, and fill weight data assessed (b) (4) were used to inform the assessment of whether each strength of ABP 798 is the same as that of US-Rituxan. Based on the comparative analytical assessment and manufacturing data, the 100 mg/10 mL and 500 mg/50 mL ABP 798 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in unit of mass per unit volume as the corresponding strengths of US-Rituxan. Each strength of ABP 798 in a vial is the same as that of US-Rituxan.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Potency (CDC)	Efficacy and Safety	Intrinsic to the molecule	(b) (4)	N/A
Potency (ADCC)	Efficacy and Safety	Intrinsic to the molecule		N/A

¹ U.S. Prescribing Information, U.S.-Licensed Rituxan, Accessed July 6, 2020 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103705Orig1s5458lbl.pdf

			(b) (4)	
Potency (CD20 binding)	Efficacy and Safety	Intrinsic to the molecule		N/A
Identity	Efficacy and Safety	Intrinsic to the molecule		N/A
High molecular weight (HMW) species/aggregates (product-related impurities)	Efficacy, Safety, Immunogenicity, and Pharmacokinetics (PK)	Can be introduced during the DS and DP manufacturing process and storage. Minimal changes are expected during storage under recommended conditions through expiry.		N/A
Fragmentation (product-related impurities)	Efficacy, Immunogenicity and PK	Can be introduced during the DS and DP manufacturing process and throughout storage.		N/A

		Minimal changes are expected during storage under the recommended conditions through expiry.	(b) (4)	
Acidic and basic charge variants (product-related impurities)	Efficacy, Immunogenicity and PK	Intrinsic to the molecule Can be impacted during the DS and DP manufacturing process and storage. Minimal changes are expected during storage under recommended conditions through expiry.		N/A
Oxidation (b) (4) (product-related impurity)	Efficacy and PK	Can be impacted by the DS and DP manufacturing process, exposure to elevated temperature, chemical oxidation, and UV light exposure. Minimal changes are expected on stability.		N/A
Deamidation (product-related impurity)	Efficacy and PK	Impacted by the DS and DP manufacturing process, exposure to elevated temperatures and physiological pH.		N/A

		Minimal change is expected on stability through expiry.	(b) (4)	
Glycosylation	Efficacy, Safety and PK	(b) (4) process		N/A
Protein concentration	Efficacy, Safety and PK	DS and DP manufacturing processes (formulation)		N/A
pH	Efficacy and Safety	Manufacturing process and formulation		N/A

			(b) (4)	
(b) (4)	Safety	Formulation process		N/A
Osmolality	Efficacy and Safety (control of degradation through formulation)	Formulation process		N/A

B. Drug Substance [rituximab-arrx] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance	Safety	Manufacturing process	(b) (4)	N/A
Host Cell Proteins (HCP) (Process-related impurities)	Safety and Immunogenicity	Production cell line		N/A
Host Cell DNA (Process-related impurities)	Safety	Production cell line		N/A

			(b) (4)	
(b) (4)	Safety and Immunogenicity	(b) (4)		N/A
(Process-related impurities)				
Residual process reagents (i.e., (b) (4))	Safety and Immunogenicity	Cell culture media, production bioreactor media, downstream process reagents.		N/A
Viruses (Contaminants)	Safety	Contamination during manufacture, most likely during cell culture operations		N/A
Mycoplasma (Contaminants)	Safety	Mycoplasma would most likely be introduced during the cell culture operations.		N/A
Leachables (Process-related impurities)	Safety	Manufacturing components and the DS container closure system.		N/A

			(b) (4)	
Bioburden	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials, manufacturing process		N/A
Endotoxin	Safety and purity	Raw materials, manufacturing process		N/A

- Description:** Rituximab-arrx is a chimeric IgG1 monoclonal antibody. The Fc regions of the heavy chains retain Fc effector functions important in the mechanisms of action of the molecule, and each have one N-linked glycosylation site. Each heavy chain consists of 451 amino acids with 4 interchain disulfide bonds. Each light chain consists of 213 amino acids with 2 intrachain disulfide bonds. The theoretical mass of the molecule is 144,243 Da. The theoretical extinction coefficient is $1.6 \text{ cm}^{-1}(\text{mg/mL})^{-1}$ and the experimental extinction coefficient is $1.7 \text{ cm}^{-1}(\text{mg/mL})^{-1}$. The experimental extinction coefficient used to release the process validation and commercial material is (b) (4). It is not clear if the theoretical or experimental extinction coefficient was used for release of early clinical material; however, the difference between the two coefficients are minor and not expected to impact the protein concentration results over the course of development.
- Mechanism of Action:** Rituximab-arrx targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes and malignant B cells. Upon binding to CD20, rituximab-arrx mediates B-cell lysis. Possible mechanisms of cell lysis include CDC, ADCC, ADCP, and apoptosis.
- Potency Assay:** The CDC bioassay is a cell-based assay that measures the rituximab-arrx dose-dependent activation of the complement cascade in WIL2-S cells expressing

CD20 on the surface leading to cell death. ADCC potency is controlled indirectly through the individual control of total afucosylated glycans (high mannose+G0+G1+G2) and afucosylation (G0+G1+G2) by glycan mapping using HILIC.

- **Reference Materials:** The rituximab-arx commercial reference standard program includes a Primary Reference Standard (PRS) derived from ABP 798 DS lot 0010177775, which was used in toxicological studies and is comparable to the clinical and commercial DS. A Working Reference Standard (WRS) will be qualified per the future reference standard qualification protocol submitted to the BLA. The PRS will be used for commercial release and stability testing until qualification and implementation of the WRS. The PRS will be used to qualify the future WRS. The need to qualify a future PRS is not expected.

- **Critical starting materials or intermediates:** (b) (4)

A two-tiered cell banking system consisting of a Master Cell Bank (MCB) and a Working Cell Bank (WCB) were established. Viability and viable cell density of the MCB and WCB are monitored as part of the cell bank annual stability protocols and during continuous process verification. Additional quality control measures have been implemented as part of the cell bank stability testing procedures to ensure consistency in the stability data reported. Adequate testing for adventitious agents was performed on the cell banks. The MCB and WCB have been demonstrated to be stable based on the totality of information and data submitted to the BLA.

- **Manufacturing process summary:** (b) (4)


(b) (4)

- **Container closure:** (b) (4)
The container closure system is suitable for rituximab-arrx DS based on stability data and maintenance of closure integrity.
- **Dating period and storage conditions:** The dating period for the DS is (b) (4) months when stored at (b) (4) °C.

C. Drug Product [Riabni] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy (b) (4)	Other
Appearance	Efficacy and Safety (stability)	Manufacturing process		N/A
Color and clarity (general)	Efficacy and Safety (stability)	Formulation, contamination or degradation		N/A
Deliverable volume (general)	Efficacy and Dosing	Manufacturing process		N/A

			(b) (4)	
Particulate Matter (visible and subvisible) (Product- or process-related impurities)	Safety and Immunogenicity	Manufacturing process and container closure system		N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and container closure system		N/A
Sterility (Contaminant)	Safety risk to patients (infection) Efficacy (degradation or modification of the product by microorganisms or their byproducts)	Contaminants could be introduced throughout DP manufacturing		N/A
Endotoxin (Contaminant)	Safety, purity, and immunogenicity	Contaminants could be introduced throughout the DP manufacturing process and through raw materials		N/A
Container Closure Integrity (Sterility Assurance)	Safety (loss of sterility due to breaches in Container Closure Integrity) or evaporation/leakage (impacting concentration or content)	Container closure breaches during DP shelf-life		N/A

- **Potency and Strength:** Riabni is supplied as 100 mg/10 mL and 500 mg/50 mL. Potency is defined as the percent activity relative to the current rituximab-arrrx PRS. The potency assay is the same as described for the DS.

- **Summary of Product Design:** Riabni is supplied in a single-dose vial as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution intended for intravenous administration, containing 100 mg or 500 mg deliverable DP. The vials contain a 10 mL or 50 mL deliverable volume of 10 mg/mL rituximab-arrx, 154 mM sodium chloride (9 mg/mL), 25 mM sodium citrate dihydrate (7.35 mg/mL), 0.07% (w/v) polysorbate 80 (0.7 mg/mL), and water for injection (WFI), at pH 6.5.
- **List of Excipients:** Sodium chloride; Sodium citrate, dihydrate; polysorbate 80; hydrochloric acid; WFI. All excipients are compendial.
- **Reference Materials:** The same reference material is used for DS and DP.
- **Manufacturing process summary:** (b) (4)
- **Container closure:** The primary container closure system for Riabni DP consists of either a 10 cc or 50 cc (b) (4) glass vial (b) (4) with a 20 mm (b) (4) elastomeric stopper (b) (4) and an aluminum seal with flip-off cap (b) (4)
- **Dating period and storage conditions:** The dating period for Riabni DP is 36 months when stored at 2°C to 8°C, protected from light.
- **List of co-package components, if applicable:** N/A

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Protect RIABNI vials from direct sunlight
- Store RIABNI vials refrigerated at 2-8°C
- Do not shake or freeze vials
- If not used immediately, store diluted RIABNI solutions as shown in Table 1.

Table 1
Diluted RIABNI Solution Storage Conditions

Diluent Used to Prepare Solution for Infusion	Diluted RIABNI Solution Storage Conditions
0.9% Sodium Chloride Injection, USP	Store RIABNI solution diluted in 0.9% Sodium Chloride Injection, USP refrigerated at 2°C to 8°C (36°F to 46°F) for up to 7 days after preparation and protect from light.
5% Dextrose Injection, USP	Store RIABNI solution diluted in 5% Dextrose Injection, USP refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours after preparation.

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture; in-process, lot release, and stability testing; Working cell bank storage; Unprocessed bulk testing: mycoplasma	Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI) 40 Technology Way, West Greenwich, Rhode Island, United States of America, 2817	3003359885	Approve based Section 704(a)(4) records review	N/A	Approve
Drug substance in-process testing: glycan map; Master cell bank and working cell bank storage; Working cell bank manufacture; Drug product lot release and stability testing	Amgen Inc. (Referred to as Amgen Thousand Oaks or ATO) One Amgen Center Drive, Thousand Oaks, California, United States of America, 91320	2026154	Approve - Based on Previous History	N/A	Approve
Drug substance in-process, lot release, and	Amgen Technology Ireland UC	3002808497	Approve - Based on Previous History	N/A	Approve

stability testing; Drug product in- process, lot release, and stability testing	(Referred to as Amgen Dun Laoghaire or ADL) Pottery Road, Dun Laoghaire, Ireland				
Mycoplasma testing (unprocessed bulk) Adventitious viral testing (unprocessed bulk)	(b) (4)		Approve - Based on Previous History	N/A	Approve
Master cell bank and working cell bank storage	Amgen Inc. (Referred to as Louisville Distribution Center or LDC) 12000 Plantside Drive, Louisville, KY, United States of America, 40299	3003750095	No evaluation necessary	N/A	N/A
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug product manufacture, Drug product in- process and lot release testing	(b) (4)		Approve based on facility profile	PLI Waived	Approve
Drug product packaging and labeling	Amgen Manufacturing Ltd (Referred to as AML) Carr 31, KM 24.6 Juncos, Puerto Rico 00777 USA	1000110364	Approve based on facility profile	N/A	Approve
Drug product packaging and labeling	Amgen Europe B.V. (Referred to as ABR)	3005889661	Approve based on facility profile	N/A	Approve

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Immunex Rhode Island Corporation (FEI 3003359885) and (b) (4) proposed for rituximab-arx drug substance and drug product manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent

relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:

- i. Protocols approved: Annual stability protocol for DS; protocol for qualification of a future WRS; protocol for qualification of future WCB; MCB and WCB stability protocols; (b) (4) protocol
- ii. Outstanding assessment issues/residual risk: None
- iii. Future inspection points to consider: An evaluation of the complete root cause analysis and deviation report(s) associated with the investigation into the ABP 798 MCB and WCB stability. Refer to BLA 761140 SDN 24. The relevant long term storage sites for the ABP 798 MCB and WCB are ATO and LDC (see Section F above for additional facilities information).

b. Drug Product

- i. Protocols approved: Annual stability protocol for DP
- ii. Outstanding assessment issues/residual risk: None
- iii. Future inspection points to consider: None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KRISTEN P NICKENS
11/04/2020 03:12:58 PM

QING ZHOU
11/04/2020 03:17:51 PM

BLA STN 761140

**RIABNI (rituximab-arrx) Injection,
100 mg/10 mL and 500 mg/50 mL (10 mg/mL)**

Amgen, Inc.

OBP Product Quality Assessment Data Sheet

1. BLA#: 761140
2. Assessment Date: October 16, 2020
3. Primary Assessment Team:

Product Quality: OBP – Amy Hsu (DS, DP, similarity, and immunogenicity)
Kristen Nickens (ATL)
Qing (Joanna) Zhou (Review Chief)
James Barlow/ Scott Dallas/ Vicky Borders-Hemphill (labeling)

OPMA – Zhong Li (DS microbiology and facility)
Amy Devlin (DP microbiology and facility)
Maxwell van Tassel (microbiology)
Than Thuy Nguyen (facility)

OPRO – Anh-Thy Ly (RBPM)

Clinical: Pamela Seam (DHM II); Juwaria Waheed (DRTM)

Pharmacology/Toxicology: Simon Williams

Clinical Pharmacology: Shalini Wickramaratne Senarath Yapa; Salaheldin Hamed

Statistics: Laura Fernandes; Yu-Ting Weng; William Koh

OND RPM: Beatrice Kallungal

4. Major GRMP Deadlines:

Filing Meeting: January 31, 2020
Mid-Cycle Meeting: May 19, 2020 (internal) and June 2, 2020 (with Sponsor)
Late-Cycle Meeting: October 7, 2020
Primary Review Date (OPQ): August 12, 2020
OPQ Integrated Quality Assessment Review Date: August 19, 2020
CDTL Memo Date: November 7, 2020
BsUFA Action Date: December 19, 2020

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request (IR) #1 (from OPMA)	January 30, 2020
OND Filing Meeting	January 31, 2020
Filing Memo	February 12, 2020
Filing Letter	February 27, 2020
IR #2 (from OPMA)	April 9, 2020
IR #3 (CAA)	April 22, 2020
OND Mid-Cycle Meeting	May 18, 2020
IR #4 (CAA)	May 21, 2020
Mid-Cycle Communication with Sponsor	June 1, 2020
IR #5 (DS and DP control strategy, etc.)	June 1, 2020
IR #6 (compatibility, etc.)	June 19, 2020
IR #7 (DS and DP control strategy, etc.)	July 1, 2020
IR #8 (DS and DP control strategy, specification, etc.)	July 29, 2020
IR #9 (MCB and WCB stability, specification, etc.)	August 7, 2020
IR #10 (WCB and WCB stability)	August 17, 2020
Late-Cycle Communication with Sponsor	September 18, 2020

IR #11 (CDC, ADCC, and glycosylation controls)	October 7, 2020
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6. Submission Assessed:

Submission:	Date Received:	Assessment Completed (yes or no)
STN 761140/0001	December 18, 2020	Yes (OBP/OPMA)
/0004 (response to IR #1)	February 4, 2020	Yes (OPMA)
/0007 (response to IR #2)	April 24, 2020	Yes (OPMA)
/0008 (response to IR #3)	May 8, 2020	Yes (OBP)
/0009 (response to IR #4)	May 27, 2020	Yes (OBP)
/0010 (response to IR #5 and follow-up to IR #1)	June 17, 2020	Yes (OBP/OPMA)
/0011 (response to IR #6)	June 29, 2020	Yes (OBP)
/0012 (response to IR #7)	July 21, 2020	Yes (OBP)
/0015 (response to IR #8)	August 11, 2020	Yes (OBP/OPMA)
/0017 (response to IR #9)	August 13, 2020	Yes (OBP)
/0024 (responses to IR #10 for MCB/WCB stability, IR #6 for IV bag compatibility study and IR #9 for CEX resin reuse protocol)	September 30, 2020	Yes (OBP)
/0025 (response to IR #11)	October 15, 2020	Yes (OBP)

7. Drug Product Name/Code/Type: Riabni/rituximab-arrx/ABP 798

8. Pharmacological Category: recombinant chimeric monoclonal IgG1 antibody targeting human CD20

9. Dosage Form: liquid

10. Strength/Potency: 100 mg/10 mL and 500 mg/50 mL (10 mg/mL)

Type of potency assay: An in-house cell-based assay that measures CD20 binding and subsequent complement-dependent cytotoxicity (CDC)

11. Route of Administration: intravenous injection

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	Adequate
			Yes	Adequate
			Yes	Adequate

13. Inspectional Activities:

The ABP 798 drug substance (DS) manufacturing facility at Amgen Rhode Island (ARI), West Greenwich, RI, USA (FEI: 3003359885) was previously inspected by FDA between April 15-19, 2019 as part of the pre-license inspection (PLI) for BLA 761086/0 (for ABP 710 DS). The ARI facility status is acceptable per the PLI, and the DS manufacturing processes are similar between BLA 761086 and BLA 761140 (for ABP 798 DS). In lieu of an on-site PLI, a Section 704(a)(4) review was conducted by Zhong Li (OPMA), Amy Hsu (OBP), and Kristen Nickens (OBP). The ARI facility status reviewed is deemed acceptable. Items recommended for future surveillance inspections for the ARI site (i.e., deviations, analytical method trending program) are included in the Section 704(a)(4) review memo documented in Panorama.

The ABP 798 drug product (DP) manufacturing facility at (b) (4) was inspected by FDA (b) (4) as part of the PLIs for BLA (b) (4). The PLI for BLA 761140 is waived based on the inspection history, licensing status, and similarity in manufacturing equipment and process steps between BLA (b) (4) and BLA 761140. The details to support the PLI waiver are documented in Panorama.

14. Consults Requested by OBP: none

15. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
X	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: none

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

I recommend approval of STN 761140/0 for ABP 798 manufactured by Amgen, Inc. The data and information provided in the submission support that the ABP 798 DS and DP manufacturing processes are adequately controlled to ensure consistent product quality and safety.

II. List of Deficiencies to be Communicated: None

III. List of Post-Marketing Commitments/Requirements: None

IV. Assessment of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

Amgen, Inc., claims categorical exclusion from the preparation of an Environmental Assessment under 21 CFR 25.31 (c), because no extraordinary circumstance exist that could significantly alter the human environment upon exposure of ABP 798.

V. Primary Container Labeling Assessment

The CMC review of DP labeling was conducted by Scott Dallas (12/19/2019-6/26/2020), James Barlow (6/27/2020-), and Vicky Border-Hemphill (6/27/2020-), OBP.

VI. Assessment of Common Technical Document- Quality Module 3.2

The review of Module 3.2 is provided below.

VII. Assessment of Immunogenicity Assays- Module 5.3.1.4

The review of Module 5.3.1.4 is provided below.

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Description of Drug Substance and Drug Product

Assessor note: Several rounds of IRs were communicated between Amgen and FDA regarding ABP 798 DS and DP manufacturing process control strategy, comparative analytical assessment (CAA), and clarifications of the information and data submitted to the BLA. Updates were made to the BLA accordingly. The memo represents the product quality assessment of the final data and information provided.

S. Drug Substance

3.2.S.1 General Information

ABP 798 (non-proprietary name: rituximab-arrx) is a biosimilar to US-licensed Rituxan, a chimeric anti-CD20 IgG1 monoclonal antibody. The variable regions including complementarity-determining regions (CDRs) are of murine origin, and the constant domains are of human origin. ABP 798 contains intra- and inter-chain disulfide bonds between the heavy chains (HC) and light chains (LC) and N-glycans (i.e., A2G0F, A2G1F) at Asn 301 in the Fc domain of each HC (Figure 1, Section S.1.2). The amino acid sequences for the HC and LC, molecular masses of glycosylated ABP 798, extinction coefficient, isoelectric point (pI), and melting temperatures (T_m) are also provided (Figures 2-3, Section S.1.2; Table 1, Section S.1.3). The mechanism of action (MOA) of ABP 798 includes CD20 binding, complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and CD20-mediated apoptosis.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

(b) (4)

3.2.S.7 Stability

Eight ABP 798 DS lots are evaluated for stability (Table 1). Two are supporting stability lots (30P130805 and 30P130916) manufactured using the ATO ^{(b) (4)} process, which have data for 12 and 60 months, respectively. Three are primary stability lots (0010244198, 0010249102, and 0010318855) manufactured using the ATO ^{(b) (4)} process, which have data for 48, 36, and 24 months, respectively. Three are production stability lots (0010356678, 0010356679, and 0010356680) manufactured using the ARI process, which all have data for 18 months. All lots are prepared at 50 mg/mL and stored ^{(b) (4)}

Assessor comment: The supporting, primary, and production stability lots represent development, clinical, and commercial/PV lots, respectively. The CCS material information is consistent with the intended CCS described in Section S.6.

The stability lots are tested under the recommended/long-term (b) (4), accelerated (5°C, ranged between 2°C and 8°C) and stressed (25°C, ranged between 23°C and 27°C) storage conditions (Tables 2-4, Section S.7.1). The lots are evaluated for appearance, color (for tracking purpose only), % main, % acidic and % basic by CEX-HPLC (acceptance criteria: (b) (4) % for % main and comparable to reference standard for acidic and basic peaks), % main and % HMW by SE-UHPLC (acceptance criteria: (b) (4) % for % main and report results for % HMW), % HC+LC by rCE-SDS (acceptance criterion: (b) (4) %), % main by nrCE-SDS (acceptance criterion: (b) (4) %), relative potency for CDC (acceptance criterion: (b) (4) %), pH (acceptance criterion: (b) (4)) (Table 5, Section S.7.1). The long-term stability data are collected at the stability zero time point or at release, every three months from 3 months to 12 months, every six months from 12 months to 60 months (18+ months data collected only for primary and production lots and the supporting lot 30P130916). The accelerated stability data are collected at the stability zero time point or at release, 0.5 month, 1 month (only for primary and production lots), 3 months, and 6 months. The stressed stability data are collected at the stability zero time point or at release, 0.25 month, 0.5 month, 1 month (only for primary and production lots), and 3 months. All of the accelerated and stressed studies are completed.

Assessor comment: *The storage temperatures, stability testing intervals, quality attributes, stability tests and associated acceptance criteria are appropriate for each storage condition.*

The shelf life of ABP 798 DS is determined based on statistical analysis of the product quality results (CEX-HPLC, SE-UHPLC, rCE-SDS, nrCE-SDS, CDC bioassay, and pH) from the supporting, primary and production stability lots under the recommended storage condition. Only lots with stability data available for at least 12 months within the proposed shelf life are used to evaluate the shelf life. The proposed shelf is (b) (4) months for ABP 798 DS, when stored at the recommended condition.

Assessor comment: *Comparability between the supporting, primary and production stability lots has been demonstrated (see Section S.2.6), thus all of these lots are representative of the intended commercial ABP 798 and appropriate to support the shelf life. Based on the information described, only the supporting lot 30P130916 (60 months of data) and the two primary lots 0010244198 and 0010249012 (48 and 36 months of data, respectively) are used to evaluate the shelf life. The approach to derive the shelf life for ABP 798 considers the minimum and maximum data values observed among the lots (i.e., worst-case). See the results in the following long-term stability data section.*

Long-term stability data:

The results for all lots are within the acceptance criteria (Tables 1-2, document entitled “Stability Data – Supporting Lots (b) (4)”; Tables 1-2, document entitled “Stability Data – Supporting Lots (b) (4)”; Tables 1-3, document entitled “Stability Data – Primary Lots (b) (4)”; Tables 1-3, document entitled “Stability Data – Production Lots (b) (4)”; Section S.7.3). The stability trending analysis results are summarized as follows:

- **Charge variants by CEX-HPLC:** The data of all lots are within specification and show no stability trend for % main, % acidic and % basic (Figures 1-6 and Table 6, Section S.7.1). The chromatograms of the supporting stability lot 30P130916 at 60 months, primary stability lot 0010244198 at 48 months, and reference standard are comparable, with respect to retention time and shape of individual peaks (Figure 7, Section S.7.1).
- **Size variants by SE-UHPLC:** The data of all lots are within specification and show minor increases in % HMW (up to 0.6% differences) and concurrent decreases in % main during the first 12 months (Figures 9-12 and Table 7, Section S.7.1). The chromatograms of the supporting stability lot 30P130916 at 60 months, primary stability lot 0010244198 at 48 months, and reference standard are comparable, with respect to retention time and shape of individual peaks (Figures 13-14, Section S.7.1). Up to 1.9% HMW species were observed (see the relevant documents in Section S.7.3).
- **Fragmentation by rCE-SDS:** The data of all lots are within specification and show no stability trend for % HC+LC (Figures 15-16 and Table 8, Section S.7.1). The electropherograms of the supporting stability

lot 30P130916 at 60 months, primary stability lot 0010244198 at 48 months, and reference standard are comparable, with respect to retention time and shape of individual peaks (Figures 17-18, Section S.7.1). The results for % LMW, % LC, % MMW, % NGH, % HC, % Post-HC, and % HMW show steady levels over time (see the relevant data tables in Section S.7.3).

- **Partially-reduced species and fragmentation by nrCE-SDS:** The data of all lots are within specification and show no stability trend for % main and % pre-peaks (Figures 19-22 and Table 9, Section S.7.1). The electropherograms of the supporting stability lot 30P130916 at 60 months, primary stability lot 0010244198, and reference standard are comparable, with respect to retention time and shape of individual peaks (Figures 23-24, Section S.7.1).
- **CDC bioassay:** The data of all lots are within specification and show no stability trend for relative potency by CDC bioassay (Figures 25-26 and Table 10, Section S.7.1).
- **pH:** The data of all lots are within specification and show no stability trend for pH (Figures 27-28 and Table 11, Section S.7.1).
- **Appearance:** All lots remain as liquid, practically free of particles throughout the testing period (see the relevant stability data tables, Section S.7.3).
- **Color:** All lots remain colorless, $\leq Y7$, or $\leq Y6$ throughout the testing period (see the relevant stability data tables, Section S.7.3).

Assessor comment: The long-term stability results support storage of ABP 798 DS at the recommended storage condition for at least the proposed shelf life of (b) (4) months.

Accelerated and stressed stability data:

The results are within the acceptance criteria (Tables 1-2, document entitled “Stability Data – Supporting Lots at 5C”; Tables 1-2, document entitled “Stability Data – Supporting Lots at 25C”; Tables 1-3, document entitled “Stability Data – Primary Lots at 5C”; Tables 1-3, document entitled “Stability Data – Primary Lots at 25C”; Tables 1-3, document entitled “Stability Data – Production Lots at 5C; Section S.7.3; Tables 1-3, document entitled “Stability Data – Production Lots at 25C; Section S.7.3). The stability trending analysis results are summarized as follows:

- **Charge variants by CEX-HPLC:** All lots show no stability trend for charge variants under the accelerated storage conditions; however, all lots exhibit a trend of increased % acidic (up to 9% differences over 3 months) with concurrent decreases in % main and % basic under the stressed storage conditions (Figures 29-34, Section S.7.1). The chromatograms of the supporting stability lot 30P130916 at 5°C for 6 months, primary stability lot 0010244198 at 0 month, and reference standard are comparable, while the primary stability lot shows increased intensity for the acidic peaks over 3 months at 25°C (Figures 35-36, Section S.7.1).
- **Size variants by SE-UHPLC:** All lots show a trend of increased % HMW (up to 1.3% differences at 5°C for 6 months and up to 1.6% differences at 25°C for 3 months) decreased % main (up to 2.8% at 25°C for 3 months) (Figures 37-40, Section S.7.1). The chromatograms show that the supporting stability lot 30P130916 at 5°C for 6 months has higher HMW content than the reference standard, and that the primary stability lot 0010244198 also has increased intensity for the HWW and LMW peaks over 3 months at 25°C (Figures 41-42, Section S.7.1).
- **Fragmentation by rCE-SDS:** All lots show no stability trend for % HC+LC at 5°C for 6 months and up to 1.4% decreases in % HC+LC at 25°C over 3 months (Figures 43-44, Section S.7.1). The electropherograms show that the supporting stability lot 30P130916 at 5°C for 6 months, primary stability lot 0010244198 over 3 months at 25°C, and reference standard have the same sets of peaks (Figures 45-46, Section S.7.1). The results for % LMW, % LC, % MMW, % NGH, % HC, % Post-HC, and % HMW show steady levels over time under the accelerated storage conditions, while minor increases in % MMW and % HMW over time (up to 0.4% differences for both) under the stressed storage conditions are noted (see the relevant data tables in Section S.7.3).

- **Partially-reduced species and fragmentation by nrCE-SDS:** All lots show no stability trend for % main and % pre-peaks at 5°C for 6 months and a trend of decreased % main (up to 1.5% differences) and increased % pre-peaks over 3 months at 25°C (Figures 47-50, Section S.7.1). The electropherograms show that the supporting stability lot 30P130916 at 5°C for 6 months has higher pre-peaks content than the reference standard, and that the primary stability lot 0010244198 also has increased intensity for pre-peaks over 3 months at 25 °C (Figures 51-52, Section S.7.1).
- **CDC bioassay:** All lots show no stability trend for relative CDC potency under either storage conditions (Figures 53-54, Section S.7.1).
- **pH:** All lots show no stability trend for pH under either storage conditions (Figures 55-56, Section S.7.1).
- **Appearance:** All lots show no stability trend for appearance under either storage conditions (see the relevant stability data tables, Section S.7.3).
- **Color:** All lots show no stability trend for color under either storage conditions (see the relevant stability data tables, Section S.7.3).

Assessor comment: The accelerated and stressed stability results indicate that the major degradation pathways of ABP 798 DS include formation of HMW and fragmented species. The observed differences do not impact on CDC potency of ABP 798 DS.

The post-approval stability testing protocol proposed for annual ABP 798 DS lots, if manufactured for the year, includes a long-term stability program and a stressed stability program (Tables 1-2, Section S.7.2).

(b) (4)

Justifications for excluding the stability tests used to generate the long-term, accelerated, and stressed stability data are provided (Table 12, Section S.7.1). The appearance, color, and pH tests are excluded, because the methods are shown not stability indicating under either storage conditions. The CEX-HPLC, rCE-SDS, nrCE-SDS, and CDC bioassay tests are excluded from the long-term stability protocol, because no stability trend is noted under the long-term and accelerated storage conditions. The nrCE-SDS test is also excluded from the stressed stability protocol, because the pre-peaks identified by nrCE-SDS are primarily reduced forms of fragmented species, which can be assessed using the rCE-SDS test (see Section S.3.1/2.5.6.2). The CEX-HPLC, rCE-SDS, and CDC bioassay tests are included in the DP release and stability specifications (see Section P.5.1).

Assessor comment: The initial post-approval protocol for DS stability lots only included an evaluation for % HMW by SE-UHPLC under long-term storage conditions and thus was inappropriate to fully capture the potential changes to product quality over time. Amgen was requested to implement an additional test for % main by SE-UHPLC and an analytical method to evaluate charge heterogeneity as part of the protocol (IR-7 and IR-8). Amgen agreed to implement a test for control of % acidic, % basic, and % main by CEX-HPLC under long-term stability conditions (Table 29, response to IR-8, SDN 15) and provided justification to monitor fragmentation using % HC+LC by rCE-SDS instead of % main by SE-UHPLC (see Section S.4.5). The post-approval test schedules, as amended, for ABP 798 DS stored under long-term and stressed conditions are appropriate.

P: Drug Product

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

The 100 mg and 500 mg dose presentations of ABP 798 DP are supplied as a sterile, preservative-free, clear-to-slightly opalescent, colorless-to-slightly yellow solution in a single-use vial for intravenous administration. Each vial contains 10 mg/mL ABP 798 (10 mL or 50 mL deliverable volume), 154 mM (9 mg/mL) sodium chloride, 25 mM (7.35 mg/mL) sodium citrate dihydrate, 0.07% w/v (0.7 mg/mL) polysorbate 80, and water for injection

(WFI), pH 6.5 (Table 1). All of the excipients and WFI are of USP grade. The DP is stored in a 10 cc (100 mg) or 50 cc (500 mg) (b) (4) glass vial, elastomeric stopper, and aluminum seal with flip-off cap.

Assessor comment: The DP description is consistent with the proposed labeling information.

3.2.P.2 Pharmaceutical Development

(b) (4)

3.2.A.3 Novel Excipients

No novel excipient is included in the ABP 798 DP.

3.2.R Regional Information (USA)

3.2.R.1 Comparative Analytical Assessment

Assessor note: *The CAA information and data were submitted in multiple documents under Section 3.2.R. For ease of review, the information and data provided to support suitability of the analytical methods used for CAA only (Section 3.2.R: Analytical Similarity Assessment – Methods Qualification Summary), all biological activity assays (see the associated method qualification documents in Section 3.2.R), and validated analytical methods (Sections S.4.3 and P.5.3) are incorporated into the description and discussion for the corresponding product quality attributes.*

Introduction (Document entitled “Analytical Similarity Assessment – Executive Summary”)

ABP 798 is as a proposed biosimilar to rituximab. Amgen is seeking the same indications as approved for US-licensed Rituxan. Two clinical studies were conducted including a supportive efficacy and safety study in

rheumatoid arthritis patients (RA: clinical study 20130108) and the pivotal comparative clinical study performed in CD20 positive B-cell non-Hodgkin's lymphoma patients (NHL: clinical study # 20130109). The pivotal comparative clinical study was performed comparing ABP 798 and US-licensed Rituxan, and the supportive RA study was performed comparing ABP 798, US-licensed Rituxan, and EU-approved rituximab (referred to as EU-approved MabThera). Comparative analytical data were provided for all three products.

Assessor comment: *ABP 798 and the US-licensed Rituxan were directly compared in the pivotal comparative clinical study, which did not include EU-approved MabThera. After discussions with the application review team, it was determined that the clinical data analysis generated from the RA study would be used to support licensure of ABP 798. Therefore, the information and data to support establishment of the analytical portion of the three-way scientific bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera are discussed throughout this memo.*

Similarity Pre-Approval Inspection (sPAI)

The sPAI for ABP 798 was waived considering the following risk assessment:

- The primary testing site used to generate the comparative analytical assessment data, Amgen Thousand Oaks (ATO), was inspected in 2016 for a sPAI. No issues were identified.
- No significant concerns in data consistency, integrity or validity were identified during the review of the comparative analytical assessment submitted to support BLA 761140.
- ABP 798 under BLA 761140 is the 5th 351(k) BLA submitted to the FDA by Amgen, which currently has 4 approved 351(k) BLAs, with the most recent approvals within the past 12 months.
- A sPAI of comparative analytical assessment data submitted to support approval of the two most recent Amgen 351(k) BLA submissions were assessed during a PAI of the Amgen Rhode Island (ARI) manufacturing site and determined acceptable (ARI is the intended commercial manufacturing site of ABP 798).

Assessor comment: *Extensive information requests focusing on analytical method qualification/ verification, and testing results were sent to the sponsor to provide assurance that the information and data used to support the comparative analytical assessment were appropriate to support licensure of the 351(k) BLA.*

Comparative Analytical Assessment Plan (Document entitled “Analytical Similarity Assessment – Testing Plan and Assessment Criteria”)

ABP 798 is developed based on the same drug product (DP) formulation and dose presentations (100 mg/vial and 500 mg/vial) as US-licensed Rituxan. Up to 26 lots of ABP 798 DP manufactured from September 2013 to April 2018, up to 37 lots of US-licensed Rituxan DP with expiry from January 2014 to May 2020, and up to 30 lots of EU-approved MabThera DP with expiry from November 2013 to May 2019 were evaluated in the comparative analytical assessment (Tables 1-3). The 26 ABP 798 DP lots were filled as a 100 mg or 500 mg dose presentation on different days from the 14 independent ABP 798 drug substance (DS) lots. The first DP lots manufactured for each independent ABP 798 DS lot represent the 14 independent ABP 798 DP lots. Ten of the independent ABP 798 DP lots were manufactured as a 100 mg dose presentation at ATO and used in the nonclinical, development, stability or clinical studies (clinical lot # 0261157, 10261157, 10261169, 10261175, 10266188, 10301975, 10324182 and 10367445; used in both RA and NHL clinical studies). The other four independent ABP 798 DP lots are process validation (PV) lots, which were manufactured at the intended commercial DP manufacturing site (b) (4); 3 lots are 100 mg/vial and 1 lot is 500 mg/vial. The 14 independent ABP 798 DP lots were selected for CAA of product quality attributes potentially impacted by the DS manufacturing process (e.g., glycosylation), and the total 26 ABP 798 DP lots including the different presentations were used to evaluate DP manufacturing process specific attributes (e.g., protein concentration). The clinical US-licensed Rituxan lots include 1 lot tested in both RA and NHL studies (500 mg), 1 lot tested in the RA study only (500 mg), and 13 lots tested in the NHL study only (100 mg and 500 mg). All of the 7 clinical EU-approved MabThera lots (500 mg) were evaluated in the RA study only.

Assessor comment: The ABP 798 DP lots are representative of the ABP 798 DS lots because DS and DP share the same liquid formulation except for protein concentration. The number of lots and lot selection for ABP 798 are appropriate considering inclusion of lots manufactured at various relevant DS/DP sites and process scales and dates of manufacture (ABP lots), as well as the selection and number of US-licensed Rituxan and EU-approved MabThera lots with various expiry dates likely to capture manufacturing variability over time; inclusion of lots of the different strengths is also appropriate. Only the 100 mg ABP 798 DP was used in the pivotal clinical study, however, this is acceptable considering that the two strengths only differ in fill volume, and comparability between the DP manufacturing processes and strengths was demonstrated (see Section P.2.3, Product Comparability – 100 mg and 500 mg [ATO to (b) (4)]). Thus, the independent ABP 798 DP lots selected are representative of the clinical ABP 798 100 mg and 500 mg lots for CAA. While justifications were provided when less than the total lots of ABP 798, US-licensed Rituxan, or EU-approved MabThera were used to generate the CAA results for individual quality attributes, it was unclear how the subsets of the total lots were selected for CAA. Amgen was requested to provide scientific justification and describe the criteria to select specific lots when less than the total number of lots were used for CAA of a single attribute (IR-3). In response to IR-3, Amgen provided the following information and data.

Information provided in the response to IR-3, SDN 8: The scientific justification for lot selection when less than the total lots are used for CAA was provided (pages 47-48 and Table 28). The subsets of the US-licensed Rituxan and EU-approved MabThera lots are selected based on available inventory to minimize complete depletion of any lots. A reduced number of US and EU lots may be used for CAA of quality attributes, in which total lots are already evaluated using an orthogonal analytical method. The subsets of the ABP 798 lots are selected based on the following criteria:

- Side-by-side comparison: A side-by-side CAA is performed to provide supplemental information for the attributes already assessed using the quantitative approach with total lots (e.g., size variants, charge heterogeneity, glycan map), or to provide CAA results for the attributes with intrinsically low lot-to-lot variability (e.g., primary structure, higher order structure, due to the identical amino acid sequence for ABP 798, US-licensed Rituxan and EU-approved MabThera). Up to 3 sets of comparisons using 3 lots of each product per set are performed (i.e., a total of up to 9 ABP 798 lots). The first comparison includes the earliest three ABP 798 development lots. The second comparison includes the subsequent development lot and the first two clinical lots. The third comparison includes three 100 mg PV lots. A reduced number of lots are used for a test, when the same attribute is also assessed using an orthogonal method with total lots, or the attribute is not expected to vary from lot to lot (e.g., primary structure, higher order structure).
- CAA for quality attributes irrelevant to the primary mechanism of action (MOA; e.g., FcγRIa binding, FcγRIIb binding, and FcγRIIIb binding): Ten lots of each product are used. The ABP 798 lots include all of the development and clinical lots plus the first lot manufactured using the commercial-scale process (i.e., the development lot at Baxter).
- CAA of extinction coefficient and disulfide structure: These two attributes are not expected to vary from lot to lot, due to the same amino acid sequence for all three products. One and two lots of each product are used for extinction coefficient and disulfide structure, respectively. The ABP 798 lots include the first development lot (for both) and the first clinical lot (not used for extinction coefficient).
- Accelerated and stressed stability studies: All of the eight 100 mg ABP 798 stability lots are included. These lots represent DP manufactured from different stages (i.e., development, clinical commercial/process validation).
- Forced degradation studies: Three lots of each product are used. The ABP 798 lots include the first three clinical lots.

Assessor comment: The justification provided for lot selection is appropriate.

The following quality attributes were evaluated for the CAA:

- Biological activity: complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) with peripheral blood mononuclear cells (PBMC), ADCC with engineered natural killer cells NK92 derived from PBMC, antibody-dependent cellular phagocytosis (ADCP), CD20 binding, Fc receptor binding (e.g., FcγRIIIa, FcRn), and C1q binding
- Primary structure: intact molecular mass of IgG1, reduced and deglycosylated molecular mass of HC and LC, amino acid sequence, post-translational modifications (PTM), disulfide bonds, glycan map, extinction coefficient, isoelectric point (pI), and identity
- Higher order structure: secondary structure, tertiary structure, and thermal stability
- Particles and aggregates: subvisible particles (SVP), submicron particles, and aggregates
- Product-related substances and impurities: size variants, fragments, partially reduced species (e.g., non-glycosylated H chain or NGHC), and charge variants
- Thermal stability and forced degradation: stability trend for product-related variants and impurities under accelerated, stressed, and forced degradation conditions including elevated temperature and UV light exposure
- General properties: protein concentration and extractable volume

The analytical methods used and the associated testing sites are provided along with the product quality attributes (Tables 4-8). A total of 11 testing sites including ATO Attributes Science (ATO AS), ATO Quality Control (ATO QC), (b) (4) Amgen Washington (AWA), Amgen British Columbia (ABC), Amgen Dun Laoghaire (ADL), (b) (4) generated data to support the CAA. The quality attributes such as CDC, ADCC, size variants, charge variants, and glycosylation were evaluated at multiple testing sites. The ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were tested side-by-side (e.g., overlays of chromatograms) or independently (e.g., protein concentration by UV280).

Assessor comment: *The product quality attributes and test methods selected for the CAA are appropriate, considering the MOA, structure and function relationship, and capability of the analytical methods used. However, insufficient information and data were provided to support adequate and consistent method performance at different testing sites when the data for a single quality attribute were generated at multiple sites. Amgen was requested to provide additional data and information (e.g., method validation, verification, qualification, or transfer results) and to specify the testing site for each lot evaluated where combined CAA results from multiple sites were reported (IR-3). The CAA data tables were updated to include the testing site(s) for each lot and the associated quality attribute evaluated (Tables 29-69, Appendix 1, response to IR-3, SDN 8). Because the method verification results for the compendial methods used were not included in the response to IR-3, a follow-up IR was conveyed to Amgen (IR-4). The information and data provided in the response to IR-3 (for non-compendial methods) and IR-4 (for compendial methods) are incorporated into the following sections for individual quality attributes and associated test methods.*

A risk-based system is utilized to rank the product quality attributes of ABP 798, US-licensed Rituxan, and EU-approved MabThera based on the potential impact on clinical efficacy, PD/PK, safety and immunogenicity and to select the statistical tools applied to each attribute (Table 5):

- Risk ranking = 1 (highest risk): CDC activity; NK92 ADCC activity
- Risk ranking = 2 (moderate risk): PMBC ADCC activity, protein concentration, CD20 binding, apoptosis, Fc receptor binding, C1q binding, primary structure (e.g., afucosylation, high mannose, galactosylation), higher order structure, quantitative content of product-related substances and impurities, and non-spherical SVP by micro-flow imaging (MFI)
- Risk ranking = 3 (lowest risk, or with results not suitable for statistical evaluation): SVP by high accuracy liquid particle counter (HIAC), submicron particles, thermal stability and forced degradation,

extractable volume, and qualitative chromatographic/electrophoretic profiles for structure and purity/impurities where the quantitative results are also evaluated (e.g., glycan map)

Assessor comment: *The risk ranking information provided for biological activity-related attributes is appropriate, considering the primary MOA involving CD20 binding and Fc receptor function (e.g., CDC, ADCC) as well as the capability of orthogonal analytical methods (e.g., the method performance of the NK92 ADCC assay is more robust than the PMBC ADCC assay, and thus the NK92 ADCC assay results are more amenable to more stringent statistical evaluation).*

Based on the risk of the product quality attributes and the quantitative/qualitative nature of the test results, the following comparative data analysis approaches are used (Table 5):

- **Equivalence test:** Performed for product quality attributes in the risk ranking category 1 (i.e., CDC potency, NK92 ADCC potency). The test is to compare the difference between the data means of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots against the equivalence acceptance criterion (EAC) derived with imbalance adjustment. Similarity for a product quality attribute/test is demonstrated when the differences between the ABP 798 lots and US, between the ABP 798 and EU lots, and between the US and EU lots are within the EAC.
- **Quality range (QR):** Performed for product quality attributes in the risk ranking category 2 or 3 with quantitative results. The upper and lower bound limits of the QR are estimated using the mean $\pm$ 3 standard deviation (SD) of at least 10 lots per US-licensed Rituxan or EU-approved MabThera. The similarity criteria are met for a product quality attribute/test when at least 90% of the ABP 798 lots were within the QRs of the US lots and of the EU lots.
- **Age-adjusted QR:** Performed for purity/impurity-related product quality attributes that change over material age, i.e., HMW and % main by SE-UHPLC, % HC+LC and % LMW+MMW by rCE-SDS, % acidic, % main and % basic by CEX-HPLC. The ABP 798 lots are evaluated across long-term stability timepoints, while the US-licensed Rituxan and EU-approved MabThera lots are evaluated at the time of material receipt and at expiry. Material age of an ABP 798 lot is defined as the time between the testing and manufacturing dates; likewise, material age of an US or EU lot is the time between the testing date and the estimated manufacturing date, which is calculated as the lot expiry date subtracted by 30 months of the published shelf life for EU-approved MabThera. The test results of each lot are plotted against the associated material age to generate a single linear regression model that yields an average product-specific slope and lot-specific intercepts to account for lot-to-lot variability for each product. The goodness of model is assessed by comparing the actual and age-adjusted results of lots measured at the end of shelf life. The age-adjusted result for each lot is calculated using the lot-specific intercept, product-specific slope, and product shelf life. The similarity criteria are met when at least 90% of the ABP 798 lots are within the age-adjusted QRs of the US lots and of the EU lots.
- **Initial time point QR:** Performed for purity/impurities-related product quality attributes that do not appear to change over shelf life, e.g., % NGHC by rCE-SDS, % pre-peaks and % main by nrCE-SDS. The similarity criteria are met when at least 90% of the ABP 798 lots are within the initial time point QRs of the US lots and of the EU lots.
- **Expectation:** This approach is based on product knowledge or method capability. The similarity criteria are met when the experimental results are consistent with the theoretical value (e.g., molecular weight values calculated based on amino acid sequence and glycosylation pattern) or within method precision (e.g., spectral similarity of the spectra profiles of higher order structure).
- **Qualitative:** This approach is used for the side-by-side evaluation of chromatograms, electropherograms, or other results for purity/impurities comparison, such as trend charts for the thermo stability and forced degradation studies.

Assessor comment: *The statistical approaches and associated scientific justifications are reasonable. The equivalence test approach, as amended (i.e., use of imbalance adjustment only for equivalence testing), is acceptable for CAA of the CDC and NK92 ADCC results (see CMC Statistics Review Memo).*

Submission of age adjusted results is not historically accepted as primary CAA data due to the manipulation of the original results, thus the age-adjusted results and QRs will be considered as supporting information to the non-adjusted CAA results. The final determination of the adequacy of the proposed QRs used, considering the actual test results, risk of the product quality attribute and additional data and information provided, will be discussed in the following sections for each product quality attribute and the associated test.

Biological Activity (Document entitled “Analytical Similarity Assessment – Biological Activity”)

All assays in which results were reported as relative to reference were evaluated against the same ABP 798 primary reference standard, lot 0010177775.

CDC activity

Method description and validation summary: The CDC activity of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is measured using the release test method (see method description in Section S.4.2). The CDC bioassay used for release testing was validated at the ADL site (see Section S.4.3). The bioassay was also qualified or transferred for use at the ATO QC, AMA, and AWA testing sites. The method qualification results for the AMA and AWA sites show a relative potency range of 60-160% for AWA and 50-160% for AMA, with a repeatability coefficient of variation (CV) of 9% for AWA and 4% for AMA, intermediate precision CV of 12% for AWA and 7% for AMA, accuracy/recovery of 110% for AWA and 101% for AMA, and linearity R^2 of 0.9979 for AWA and 0.99956 for AMA (Table 8, response to IR-3, SDN 8). The method transfer summary to support the transfer from the AWA Functional Biocharacterization (AWA FB) to ATO QC sites show relative potency values of 102.887-103.818% for the DS, 101.274-105.475% for the PRS and 64.689-76.232% for the blinded ABP 798 DS lot, with an intermediate CV of 11.0% for the DS (Tables 3-5, Report # 497039, Section 1.11.1, SDN 8). The transfer was performed in three runs by one analyst on three different days using the ABP 798 DS lot # 30P130916, PRS, and blinded sample prepared under degradation conditions (DS lot # 30P130617, at 10.5 mg/mL).

Assessor comment: *See Section S.4.3 regarding the adequacy of the method validation results at ADL provided. Validation of the CDC bioassay was only performed using ABP 798. However, considering that the ABP 798, US, and EU lots share the identical amino acid sequence and DP formulation (i.e., same sample matrix), the method performance for the US and EU lots is expected to be similar to that of the ABP 798 lots. The conditions implemented for the degradation sample (“blinded ABP 798 DS lot) were not described, however, the condition appears sufficient to demonstrate that the CDC method can detect a decrease in ABP 798 product potency. Overall, the method validation, qualification, and transfer information and data provided support consistent method performance across all testing sites.*

CAA lots and test results: The total independent ABP 798 lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera. Data were generated at the ATO QC, AMA, AWA, and ADL sites. The ABP 798, US, and EU lots have a relative potency of 94-115%, 89-118% and 89-116%, respectively (Table 1 and Figure 1). The 90% confidence intervals (CI) on the difference in mean CDC relative potency of all ABP 798 lots are within the US-based EAC of $\pm 13.23\%$ (Table 6 and Figure 6) and the EU-based EAC of $\pm 14.42\%$ (Table 7 and Figure 7). The 90% CI results of the EU lots are also within the US-based EAC (Table 8 and Figure 8).

Assessor comment: *See CMC Statistics Review Memo regarding the adequacy of the equivalence test approach and results. From the product quality perspective, the relative potency for CDC results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

NK92 ADCC activity

Method description and qualification summary: The NK92 ADCC assay measures ADCC between the engineered effector NK92 cells expressing FcγRIIIa (158V) and the fluorescently labeled calcein-loaded WIL2-S target cells, which results in lysis of WIL2-S cells and release of the fluorescent calcein molecules (see Figure 42, Section S.3.1). NK92 ADCC activity is determined by the change in fluorescence intensity of the fluorescent calcein molecules released. ABP 798 induces NK92 ADCC activity via CD20 binding and Fc binding activity. The NK92 ADCC assay qualification results for the AWA and ATO AS sites show a relative potency range of 60-160% for both sites, with a repeatability CV of 4.3% for AWA and 5.2% for ATO AS, intermediate precision CV of 6.8% for AWA and 6.7% for ATO AS, accuracy/recovery of 99.6% for AWA and 99.7% for ATO AS, linearity R^2 of 0.9974 for AWA and 0.9996 for ATO AS, and specificity only when CD20-expressing WIL2-S cells and ABP 798 were used (both sites: Table 9, response to IR-3, SDN 8; ATO AS: Report # RPT-417307). The intermediate precision and accuracy results were calculated from the linearity results of the five relative potency values across the validated range, which were generated in three runs per potency level and by five analysts. The dose-response curves of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were also provided (Figure 2, Report # RPT-417307).

Assessor comment: *The dose-response curves provided support good curve fitting and consistent results between ABP 798, US-licensed Rituxan, and EU-approved MabThera. The method qualification results support consistent method performance across all testing sites.*

CAA lots and test results: The total independent ABP 798 lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera. Data were generated at the ATO and AWA sites. The ABP 798, US, and EU lots have a relative potency of 78-95%, 68-105% and 70-119%, respectively (Table 5 and Figure 5). The 90% CI on difference in mean NK92 ADCC relative potency of all ABP 798 lots are within the US-based EAC of $\pm 11.03\%$ (Table 6 and Figure 6) and the EU-based EAC of $\pm 8.95\%$ (Table 7 and Figure 7). The 90% CI results of the EU lots are also within the US-based EAC (Table 8 and Figure 8).

Assessor comment: *See CMC Statistics Review Memo regarding the adequacy of the equivalence testing approach and evaluation of the results. From the product quality perspective, the relative NK92 ADCC activity results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

PBMC ADCC activity

Method description and qualification summary: The PBMC ADCC assay measures ADCC between PBMC effector cells and the CHO target cells. The PBMCs are freshly prepared from healthy donors that express either FcγRIIIa 158 (V/V) or FcγRIIIa 158 (V/F). The target CHO cells are genetically engineered to constitutively express CD20 and luciferase genes. ADCC results in lysis of the target cells and release of luciferase protein (Figures 9-10). The amount of luciferase protein released is quantified using the commercial Steady-Glo luciferase assay kit. ADCC activity is determined by the change in luminescence intensity. ABP 798 induces PBMC ADCC activity via CD20 binding and Fc function. The PBMC ADCC assay qualification results with ABP 798 (test sample and reference standard) show a relative potency range of 50-200%, with a repeatability CV of 4.0% (from four replicates), intermediate precision CV of 8.0% (from three runs), accuracy/recovery of 103.0%, linearity R^2 of 0.9890, and specificity to ABP 798 over the negative control trastuzumab (Report # RPT-455443). The method was also qualified using EU-approved MabThera (test sample and reference standard), which yields similar results to the ABP 798 results. The dose-response curves of the ABP 798 and EU-approved MabThera lots are also provided (Appendix E, Report # RPT-455443).

Assessor comment: *The dose-response curves provided support good curve fitting of the PBMC ADCC results for ABP 798, US-licensed Rituxan and EU-approved MabThera, considering the same sample matrix (i.e., DP formulation). The specificity sample trastuzumab is a non-CD20 binding monoclonal antibody that is not expected*

to induce ADCC between PBMC and CD20-expressing CHO cells. The method qualification results provided support the PBMC ADCC assay is suitable for the intended purpose.

CAA lots and test results: The total independent ABP 798 lots were assessed against 14 lots each of US-licensed Rituxan and EU-approved MabThera. Data were generated at the AA site. The ABP 798, US, and EU lots have a relative potency of 61-93%, 59-96% and 54-98%, respectively (Table 9 and Figure 11). All ABP 798 lots are within the US-based QR of 43.7-108.9% (Figure 12) and the EU-based QR of 36.3-115.8% (Figure 13). All EU lots are also within the US-based QR (Figure 14).

Assessor comment: The PBMC ADCC assay is an orthogonal method to the NK92 ADCC assay, in which the total lots for each product were used for CAA. Thus, it is acceptable to use the subsets of the total US and EU lots for the PBMC ADCC assay. The PBMC ADCC results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

ADCP activity

Method description and qualification summary: This assay measures ADCP between the FcγRIIIa expressing (131H)-nuclear factor of activated T cells (NFAT) driven luciferase reporter Jurkat cells as the effector cells and CD20-positive Raji cells as the target cells (Figures 15-16). The luciferase reporter gene expression levels are quantified using the commercial Bright-Glo assay kit. ADCP activity is determined by change in luminescence intensity of the luciferase reporter. ABP 798 induces ADCP activity via CD20 binding and Fc function. The ADCP assay qualification results show a relative potency range of 40-250%, with a repeatability CV of 3.1% (from 10 samples), intermediate precision CV of 5.8%, accuracy/recovery of 101.1%, linearity R^2 of 0.9972, and specificity to ABP 798 over the negative control IgG1 mAb (Report # RPT-424439). The intermediate precision and accuracy results were calculated from the linearity results of seven relative potency values across the validated range, which were generated by one analyst in two, three or five runs per potency level on different days, i.e., five runs for 100% relative potency, two runs each for 60% and 150% relative potency.

Assessor comment: The dose-response curve of ABP 798 (Figure 16) support good curve fitting of the ADCP results for ABP 798, US-licensed Rituxan, and EU-approved MabThera, considering the same sample matrix for the three products (i.e., same DP formulation). The method qualification results support suitability of the ADCP assay for the intended purpose.

CAA lots and test results: The total independent ABP 798 DP lots were assessed against 36 US lots (one lot exhausted at the time of testing) and the total EU lots. Data were generated at the ATO site. The ABP 798, US, and EU lots have a relative potency of 87-109%, 90-107% and 90-109%, respectively (Table 10 and Figure 17). All ABP 798 lots are within the US-based QR of 84.8-112.7% (Figure 18) and the EU-based QR of 86.4-111.6% (Figure 19). All EU lots are also within the US-based QR (Figure 20).

Assessor comment: The ADCP results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

CD20 binding

Method description and qualification summary: The CD20 binding assay measures the competitive binding between the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) and the fluorescently-labeled ABP 798 detection reagent for CD20-expressing human B-lymphoblastoid WIL2-S cells. CD20 binding potency is determined by the change in fluorescence intensity of the labeled ABP 798 molecules (Figures 21-22). The CD20 binding assay qualification results show a relative potency range of 60-160%, with a repeatability CV of 7.0% (from 20 samples), intermediate precision CV of 6.3%, accuracy/recovery of 99.0%, linearity R^2 of 0.9991, and specificity to ABP 798 over the negative controls, two other IgG1 mAb products with different targets (Report # RPT-426662). The intermediate precision and accuracy results were calculated from the linearity

results of five relative binding levels across the validated range, which were generated in six runs per relative binding level by one analyst and in three runs by the other analyst on different days. The dose-response curves of the ABP 798 and EU-approved MabThera lots were also provided to support specificity of the assay (Figure 1, Report # RPT-426662).

Assessor comment: *The dose-response curves provided support good curve fitting of the CD20 binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera, considering the same sample matrix (i.e., DP formulation). The method qualification results support suitability of the CD20 binding assay for the intended purpose. However, it was unclear where the method was qualified, because AWA and ATO were both listed as the testing sites (IR-3). Amgen clarified that the CD20 binding assay was only performed at the ATO AS site (page 28, response to IR-3, SDN 8). The response is acceptable.*

CAA lots and test results: The total independent ABP 798 lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera. Data were generated at the ATO AS site. The ABP 798, US, and EU lots have a relative potency of 91-106%, 91-106% and 86-106%, respectively (Table 11 and Figure 23). All ABP 798 lots are within the US-based QR of 87.1-111.3% (Figure 24) and the EU-based QR of 82.1-114.1% (Figure 25). Ninety-seven percent of the EU lots are within the US-based QR (Figure 26).

Assessor comment: *The relative CD20 binding results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Apoptosis

Method Description and qualification summary: The apoptosis assay measures caspase-3/7 activity in B-cell lymphoma SU-DHL-4 cells in the presence of Caspase-Glo and luciferase, and apoptosis activity is measured by the change in luminescence intensity (Figures 27-28). ABP 798 induces apoptosis activity via CD20 binding and Fc function. The apoptosis assay qualification results show a relative potency range of 60-160%, with a repeatability CV of 7.3% (from 32 samples), intermediate precision CV of 7.4%, accuracy/recovery of 100.7%, linearity R^2 of 0.9991, and specificity to ABP 798 over the negative control, a non-CD20 binding IgG1 antibody (Report # RPT-418886). The intermediate precision and accuracy results were calculated from the linearity results of four relative potency values across the validated range, which were generated in four runs each by two analysts on different days.

Assessor comment: *The dose-response curve of ABP 798 (Figure 28) supports good curve fitting of the apoptosis results for ABP 798, US-licensed Rituxan, and EU-approved MabThera, considering the same sample matrix for the three products (i.e., same DP formulation). The method qualification results support suitability of the apoptosis assay for the intended purpose.*

CAA lots and test results: The total independent ABP 798 lots were assessed against 35 US lots (two lots exhausted at the time of testing) and the total EU lots. Data were generated at the ABC site. The ABP 798, US, and EU lots have a relative potency of 86-104%, 83-108% and 83-108%, respectively (Table 12 and Figure 29). All ABP 798 lots are within the US-based QR of 81.6-116.4% (Figure 30) and the EU-based QR of 85.4-112.9% (Figure 31). All EU lots are also within the US-based QR (Figure 32).

Assessor comment: *The relative apoptosis activity results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

FcRn binding

Method description and qualification summary: The FcRn binding assay measures competitive binding interactions between the Fc domain of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved

MabThera) and Fc-coated beads for binding FcRn-coated beads, in which increased ABP 798 concentrations result in decreased AlphaScreen signals between the Fc- and FcRn-coated beads (Figures 33-34). The FcRn assay qualification results show a relative potency range of 60-160%, with a repeatability CV of 6.1% (from 19 samples), intermediate precision CV of 9.0%, accuracy/recovery of 98.3%, linearity R^2 of 0.9911, and specificity to a human IgG antibody over the negative control bovine serum albumin (BSA) (Report # RPT-423888). The intermediate precision and accuracy results were calculated from the linearity results of five relative binding levels across the validated range, which were generated in three runs per relative binding level each by two analysts on different days. The dose-response curves of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were also provided (Figure 2, Report # RPT-423888).

Assessor comment: *The dose-response curves provided support good and consistent curve fitting of the FcRn binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera. The method qualification results support suitability of the FcRn binding assay for the intended purpose.*

CAA lots and test results: The total independent ABP 798 lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera. Data were generated at the ATO site. The ABP 798, US, and EU lots have a relative potency of 89-106%, 93-111% and 92-111%, respectively (Table 13 and Figure 35). All ABP 798 lots are within the US-based QR of 85.9-112.5% (Figure 36) and the EU-based QR of 87.1-110.1% (Figure 37). All EU lots are also within the US-based QR (Figure 38).

Assessor comment: *The relative FcRn binding results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

C1q binding

Method Description and qualification summary: The C1q assay measures the binding interactions between the Fc domain of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) and anti-C1q-horseradish peroxidase (HRP) conjugated antibody, which interactions are reported via the HRP reaction of the 3,5,3',5'-tetramethylbenzidine (TMB) substrate (Figures 39-40). The C1q binding assay qualification results show a relative potency range of 60-160%, with a repeatability CV of 4.7% (from 15 samples), intermediate precision CV of 6.2%, accuracy/recovery of 98.4%, linearity R^2 of 0.9831, and specificity to IgG1 over the negative control, an IgG2/4 hybrid antibody (Report # 426694). The intermediate precision and accuracy results were calculated from the linearity results of five relative binding levels across the validated range, which were generated in two runs per relative binding level by one analyst and in one run by the other analyst on different days. The dose-response curves of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were also provided (Figure 2, Report # RPT-426694).

Assessor comment: *The dose-response curves provided support good and consistent curve fitting of the C1q binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera. The method qualification results support suitability of the C1q binding assay for the intended purpose.*

CAA lots and test results: The total independent ABP 798 lots were assessed against 36 US lots (one lot exhausted at the time of testing) and the total EU-approved MabThera lots. Data were generated at the ATO site. The ABP 798, US, and EU lots have a relative potency of 85-106%, 67-111% and 82-107%, respectively (Table 14 and Figure 41). All ABP 798 lots were within the US-based QR of 65.4-118.9% (Figure 42) and the EU-based QR of 75.6-108.2% (Figure 43). All EU lots were also within the US-based QR (Figure 45).

Assessor comment: *The relative C1q binding results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

FcγRIa binding

Method description and qualification summary: The FcγRIa binding assay is based on the similar AlphaLISA platform as the FcRn binding assay (Figure 45). The FcγRIa binding assay qualification results show a relative potency range of 50-200%, with a repeatability CV of 2.0%, intermediate precision CV of 3.1%, accuracy/recovery of 101.3%, linearity R^2 of 0.9990, and specificity to human IgG1 over the negative control, an IgG1 Stable Effector Function Less (SEFL) molecule lacking core Fc glycan (Report # RPT-424567). The intermediate precision and accuracy results were calculated from the linearity results of seven relative binding levels across the validated range, which were generated in three runs per relative binding level each by two analysts on different days. The dose-response curves of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were also provided (Figure 2, Report # RPT-424567).

Assessor comment: *The dose-response curves provided support good and consistent curve fitting of the FcγRIa binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera. The method qualification results support suitability of the FcγRIa binding assay for the intended purpose.*

CAA lots and test results: Ten independent ABP 798 lots were assessed against 10 lots each of US-licensed Rituxan and EU-approved MabThera. Data were generated at the ATO site. The ABP 798, US, and EU lots have a relative potency of 94-103%, 85-99% and 87-99%, respectively (Table 15 and Figure 46). All ABP 798 lots are within the US-based QR of 81.6-108.3% (Figure 47) and the EU-based QR of 85.1-105.1% (Figure 48). All EU lots are also within the US-based QR (Figure 49).

Assessor comment: *The FcγRIa binding results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

FcγRIIa (131H) binding

Method Description and qualification summary: The FcγRIIa (131H) binding assay is based on the similar AlphaLISA platform as the FcRn binding assay (Figure 50). The FcγRIIa (131H) binding assay qualification results show a relative potency range of 50-200%, with a repeatability CV of 4.2% (from 15 samples), intermediate precision CV of 8.3%, accuracy/recovery of 98.9%, linearity R^2 of 0.9936, and specificity to human IgG1 over the negative control, an IgG1 SEFL molecule lacking Fc glycan (Report # RPT-426573). The intermediate precision and accuracy results were calculated from the linearity results of seven relative binding levels across the validated range, which were generated in four runs per relative binding level by one analyst and one run each by two other analysts on different days. The dose-response curves of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were also provided (Figure 2, Report # RPT-426573).

Assessor comment: *The dose-response curves provided support good and consistent curve fitting of the FcγRIIa (131H) binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera. The method qualification results support suitability of the FcγRIIa (131H) binding assay for the intended purpose.*

CAA lots and test results: The total independent ABP 798 lots were assessed against 36 US lots (one lot exhausted at the time of testing) and the total EU-approved MabThera lots. Data were generated at the ATO site. The ABP 798, US, and EU lots have a relative potency of 87-103%, 84-109% and 84-106%, respectively (Table 16 and Figure 51). All ABP 798 lots are within the US-based QR of 78.4-113.2% (Figure 52) and the EU-based QR of 78.4-112.8% (Figure 53). All EU lots are also within the US-based QR (Figure 54).

Assessor comment: *The FcγRIIa (131H) binding results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

FcγRIIb binding

Method description and qualification summary: The FcγRIIb binding assay is based on the similar AlphaLISA platform as the FcRn binding assay (Figure 55). The FcγRIIb binding assay qualification results show a relative potency range of 50-200%, with a repeatability CV of 2.2%, intermediate precision CV of 2.4%, accuracy/recovery of 104.1%, linearity R^2 of 0.9975, and specificity to human IgG1 over the negative control, an IgG1 SEFL molecule lacking core Fc glycan (Report # RPT-424402). The intermediate precision and accuracy results were calculated from the linearity results of seven relative binding levels across the validated range, which were generated in three runs per relative binding level by one analyst on different days. The dose-response curves of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were also provided (Figure 2, Report # RPT-424402).

Assessor comment: *The dose-response curves provided support good and consistent curve fitting of the FcγRIIb binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera. The method qualification results support suitability of the FcγRIIb binding assay for the intended purpose.*

CAA lots and test results: Ten independent ABP 798 lots were assessed against 10 lots each of the US-licensed Rituxan and EU-approved MabThera. Data were generated at the ATO site. The ABP 798, US, and EU lots have a relative potency of 92-101%, 89-101% and 91-109%, respectively (Table 16 and Figure 56). All ABP 798 lots are within the US-based QR of 85.4-105.9% (Figure 57) and the EU-based QR of 81.6-116.2% (Figure 58). Ninety percent of the EU lots were within the US-based QR (Figure 59).

Assessor comment: *The FcγRIIb binding results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

FcγRIIIa (158V) binding

Method description and qualification summary: The FcγRIIIa (158V) binding assay is based on the similar AlphaLISA platform as the FcRn binding assay (Figures 60-61). The method was initially qualified at the AWA site using a representative IgG1 antibody and then qualified at the ATO AS site using ABP 798 (page 5, response to IR-4, SDN 9). The FcγRIIIa binding assay qualification results for the AWA and ATO AS testing sites show a relative potency range of 50-200% for both sites, with a repeatability CV of 3.8% for AWA and 2.7% for ATO AS, intermediate precision CV of 5.0% for AWA and 6.8% for ATO AS, accuracy/recovery of 99.3% for AWA and 97.0% for ATO AS, linearity R^2 of 0.9990 for AWA and 0.9986 for ATO AS, and specificity to human IgG1 over the negative control, an IgG SEFL molecule lacking core Fc glycan (both sites: Table 10, response to IR-3, SDN 8; ATO AS: Report # RPT-423977). The intermediate precision and accuracy results were calculated from the linearity results of seven relative binding levels across the validated range, which were generated in three runs per relative binding level each by two analysts and two runs by another analyst on different days. The dose-response curves of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were also provided (Figure 2, Report # RPT-423977). The trend chart for the control shows that the relative potency values for the AWA and ATO AS sites were within 70-130% (Figure 1, response to IR-4, SDN 9).

Assessor comment: *The dose-response curves provided support good and consistent curve fitting of the FcγRIIIa (158V) binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera. The method qualification results and trend chart provided support consistent method performance across all testing sites.*

CAA lots and test results: The total independent ABP 798 lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera. Data were generated at the ATO AS and AWA sites. The ABP 798, US, and EU lots have a relative potency of 76-105%, 65-97% and 67-97%, respectively (Table 18 and Figure 62). Twelve of the 14 (86%) ABP 798 lots were within the US-based QR of 53.9-102.5%, and the two outliers are 2% higher than the upper bound (Figure 63). The ABP 798 lots yielding outlier results include one clinical lot and one development lot with relative potency of 105% for both. All ABP 798 lots were within the EU-based QR of 55.7-106.9% (Figure 64). All EU lots were within the US-based QR (Figure 65).

Assessor comment: The observed differences in relative FcγRIIIa (158V) binding were only marginally outside the QR (2.5% higher) and do not show a correlation with an impact on CDC, ADCC, ADCP, apoptosis, and total afucosylation. Considering the totality of the information and data provided, the results do not preclude a demonstration of highly similar and the establishment of the three-way scientific bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

FcγRIIIa (158F) binding

Method description and qualification summary: The FcγRIIIa (158F) binding assays is based on the similar AlphaLISA platform as the FcRn binding assay (Figure 66). The FcγRIIIa (158F) binding assay qualification results show a relative potency range of 50-200%, with a repeatability CV of 3.3%, intermediate precision CV of 6.5%, accuracy/recovery of 99.4%, linearity R^2 of 0.9969, and specificity to human IgG1 over the negative control, an IgG1 SEFL molecule lacking core Fc glycan (Report # RPT-426748). The intermediate precision and accuracy results were calculated from the linearity results of seven relative binding levels across the validated range, which were generated in one run per relative binding level by one analyst, three runs by the second analyst, and two runs by the third analyst on different days. The dose-response curves of the ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were also provided (Figure 2, Report # RPT-426748).

Assessor comment: The dose-response curves provided support good and consistent curve fitting of the FcγRIIIa (158F) binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera. The method qualification results support suitability of the FcγRIIIa (158F) binding assay for the intended purpose.

CAA lots and test results: The total independent ABP 798 lots were assessed against 35 US-licensed Rituxan lots (2 lots exhausted at the time of testing) and the total EU-approved MabThera lots. Data were generated at the ATO site. The ABP 798, US, and EU lots have a relative potency of 79-102%, 67-108% and 64-101%, respectively (Table 19 and Figure 67). All ABP 798 lots are within the US-based QR of 53.9-107.7% (Figure 68) and the EU-based QR of 52.6-108.5% (Figure 69). All EU lots are also within the US-based QR (Figure 70).

Assessor comment: The FcγRIIIa (158F) binding results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

FcγRIIIb binding

Method description and qualification summary: The FcγRIIIb assay measures the equilibrium dissociation constant (K_D) of the binding interactions between the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) and the FcγRIIIb-coated chip on a BiaCore SPR system. The raw sensorgrams are fitted using a steady-state affinity model to determine the K_D . Relative binding activity is derived by dividing the K_D of the test sample to the K_D of the reference standard. The FcγRIIIb binding assay qualification results with ABP 798 (lot # 0010177775, as the test sample and reference standard) show a relative potency range of 70-143%, with a repeatability CV of 3.1%, intermediate precision CV of 4.1%, accuracy ($\leq 7.4\%$ inaccuracy), linearity R^2 of 0.9973, and specificity to ABP 798 over the negative control, an IgG F(ab)'2 fragment (Report # RPT-455349). The assay was also qualified using EU-approved MabThera (lot # N7089B05, as the test sample and reference standard). The sensorgrams and dose-response curves of the ABP 798 and EU-approved MabThera lots were provided (Appendix A and Appendix B, Report # RPT-455349).

Assessor comment: The sensorgrams and dose-response curves of ABP 798 and EU-approved MabThera support good curve fitting of the FcγRIIIb binding results for ABP 798, US-licensed Rituxan, and EU-approved MabThera, considering the same sample matrix for the three products (i.e., same DP formulation). The method qualification results support suitability of the FcγRIIIb binding assay for the intended purpose.

CAA lots and test results: Ten independent ABP 798 lots were assessed against 10 lots each of US-licensed Rituxan and EU-approved MabThera. Data were generated at the (b) (4) site. The ABP 798, US, and EU lots have a relative potency of 81-109%, 74-109% and 70-101%, respectively (Table 20 and Figure 71). All ABP 798 lots are within the US-based QR of 63.9-118.3% (Figure 72) and the EU-based QR of 64.1-110.9% (Figure 73). All EU lots are also within the US-based QR (Figure 74).

Assessor comment: The *FcγRIIIb* binding results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

Size and Charge Variants and Associated Impurities (Document entitled “Comparative analytical Assessment – Product-related Substances and Impurities”)

Size-related variants and impurities detected by SE-UHPLC

Method description and validation/qualification summary: The levels of monomeric and HMW species in the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) are assessed using the release testing by SE-UHPLC method (see method description in Section S.4.2). The method was validated for release testing at the ADL testing site (see Section S.4.3). The method was also qualified for use at the ATO AS, AMA, and AWA sites and transferred from the ATO AS to ATO QC sites. The method transfer was stated to be waived per USP <1224>, based on the experience of the ATO QC site with the SE-UHPLC method (Table 7 and page 19, response to IR-3, SDN 8). The method qualification results for the ATO AS, AMA and AWA sites show repeatability CV of ≤0.1% for the main and HMW peaks at all sites and intermediate precision CV of <0.1% for the main and HMW peaks at the ATO AS and AMA sites and of 0.2% for both peaks at the AWA site (Table 17, response to IR-3, SDN 8).

Assessor comment: See Section S.4.3 regarding the adequacy of the method validation results for the SE-UHPLC method for testing of ABP 798 at the ADL testing site. The additional method qualification results support consistent method performance across the ADL, ATO AS, AMA, and AWA sites. However, we do not agree with the waiver justification to support not performing method transfer studies for a non-compendial method at the ATO QC testing site. Amgen was requested to provide additional information and data to support that the SE-UHPLC method is appropriately validated at the ATO QC site (IR-4). In response to IR-4, Amgen provided the following information and data.

Information and data provided in the response to IR-4, SDN 9: The method trend charts of the PRS at ATO AS and ATO QC were provided (Figures 2-3). The % HMW results are approximately 1.1% for both sites. The % monomer results are 98.9±0.1% for ATO AS and 99.0%±0.1% for ATO QC.

Assessor comment: The trend charts of the PRS support consistent performance of the SE-UHPLC method at ATO AS and ATO QC.

CAA lots and test results: The total independent ABP 798 lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera. The SE-UHPLC profiles of 9 lots each of the ABP 798, US and EU lots were also assessed in three side-by-side comparisons. Data were generated at the ATO, AMA, AWA, and ADL sites. The chromatograms show that the peak shape and distribution of the HMW peaks of the ABP 798 lots are slightly different from the HMW profiles of the US and EU lots, while consistent retention times were observed for the main and LMW peaks (Figures 1-3). The % HMW and % monomer data of the ABP 798, US and EU lots show up to 2% variability across material ages (Figures 4-5). The non-adjusted (i.e., initial time point) and age-adjusted data for % HMW and % monomer are provided in tabulated and graphic formats. The non-adjusted and age-adjusted results of the 3 ABP 798 lots aged 36 months and 1 US and 3 EU lots aged 30 months are consistent, and the linear regression parameter estimates (i.e., product-specific slope, lot-specific intercept) and plots are also provided (Tables 24-25 and Figures 68-69).

Assessor comment: *The chromatographic profiles of ABP 798, US-licensed Rituxan, and EU-approved MabThera indicate a minor difference in the HMW species. The comparison of non-adjusted and adjusted results support the suitability of the age adjustment model for SE-UHPLC analysis.*

The non-adjusted % HMW results are 0.8-1.5% for ABP 798, 0.6-1.6% for US-licensed Rituxan, and 0.6-1.3% for EU-approved MabThera, and the non-adjusted % monomer data are 98.5-99.2% for ABP 798, 98.3-99.2% for US-licensed Rituxan, and 98.5-99.2% for EU-approved MabThera (Tables 31-32 and Figures 75-76). Twelve of the 14 (86%) ABP 798 lots are within the US-based QRs of 0.43-1.47% for the HMW peaks and 98.42-99.48% for the monomer peak (Figures 77-78). For % monomer results all ABP 798 lots are within the EU-based QR of 98.44-99.40%, and for % HMW results 12 of the 14 (86%) ABP 798 lots were within the EU-based QR of 0.46-1.46% (Figures 79-80). All EU lots are within the US-based QRs for % HMW and % monomer (Figures 81-82). The two ABP 798 outliers are both clinical lots with 0.03% HMW above the upper bound of the US-based QRs; similar differences are observed with respect to the EU-based QR.

The age-adjusted % HMW results are 1.3-2.2% for ABP 798, 0.8-1.7% for US-licensed Rituxan, and 0.9-1.5% for EU-approved MabThera, and the age-adjusted % main data are 97.5-98.5% for ABP 798, 98.2-99.0% for US-licensed Rituxan, and 98.3-99.0% for EU-approved MabThera (Tables 2-3 and Figures 6-7). Ten of the 14 (71%) ABP 798 lots are within the US-based QRs of 0.68-1.56% for % HMW and 98.29-99.18% for % main, and within the EU-based QRs of 0.62-1.64% for % HMW and 98.21-99.22% for % main (Figures 8-11). All EU lots are within the US-based QR (Figures 12-13). The four ABP 798 outliers include three clinical lots and one development lot with 0.54%, 0.24%, 0.64%, and 0.24% HMW above the upper bound of the US-based QR, respectively.

Assessor comment: *The non-adjusted and age-adjusted SE-UHPLC results indicate a minor difference in the HMW content and the composition of the HMW species of ABP 798 against US-licensed Rituxan and EU-approved MabThera. Overall, while the non-adjusted data show 86% of ABP 798 lots within the US QR, the two lots outside of the QR have slightly higher HMW species content, which would not be a concern with respect to safety or immunogenicity. Also, considering the additional data and information from the HMW species characterization studies (see the following sections), the observed differences in the SE-UHPLC results do not preclude a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Size-related variants and impurities detected by size exclusion chromatography with static light scattering detection (SE-HPLC-SLS)

Method description and qualification summary: The levels of monomeric/main, HMW and LMW species in the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) are assessed using SE-HPLC-SLS. The method was qualified at the ATO AS and (b) (4) testing sites, using ABP 798 and an IgG2/4 antibody, respectively; BSA was also assessed at both sites (pages 7-8, response to IR-4, SDN 9). The method qualification results for ATO AS show no assay interference from formulation buffer (for specificity), repeatability CV of 0.4% for monomer and 2.5% for HMW, intermediate precision CV of 0.6% for monomer and 5.9% for HMW, and accuracy of within 1.5% of the monomer molar mass (Table 27, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”). The method qualification results for (b) (4) show a repeatability CV of 0.1% for monomer and 1.0% for HMW, intermediate precision CV of 0.3% for monomer and 10.1% for HMW, and accuracy of within 1.0% of the monomer molar mass (Table 18, response to IR-3, SDN 8). The BSA monomer qualification results are repeatability CV of 0.4% for ATO AS and 0.1% for (b) (4), intermediate CV of 1.0% for ATO AS and 0.8% for (b) (4) and accuracy of -2.7% for ATO AS and -3.0% for (b) (4) relative to the theoretical molecular weight of BSA (Table 2, response to IR-4, SDN 9). The BSA HMW qualification results are a repeatability CV of 2.3% for ATO AS and 0.3% for (b) (4) and an intermediate CV of 3.5% for ATO AS and 2.0% for (b) (4).

Assessor comment: *The IgG2/4 antibody and ABP 798 have comparable molecular weight, and HMW species are present in both molecules. Further considering the mechanism of the assay, the IgG2/4 antibody is sufficiently representative of ABP 798 for the SE-HPLC-SLS assay qualification analysis. The results using ABP 798, the IgG2/4 antibody, and BSA indicate that method performance of the SE-HPLC-SLS method is independent of molecules used. The method qualification summary provided and the chromatograms of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support the suitability of the SE-HPLC-SLS method for the intended purpose. The method qualification results support consistent method performance across all testing sites.*

CAA lots and test results: A total of 9 lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were evaluated in three side-by-side comparisons. The SE-HPLC-SLS profiles of the ABP 798, US and EU lots evaluated were consistent for the main and LMW peaks, whereas the HMWb peak is the predominant HMW species for ABP 798 and the HMW_a and HMW_c peaks are the major HMW species for the US and EU lots (Figures 14-15 and Table 4). The monomer molecular masses observed were 146-147 kDa for ABP 798, 147 kDa for US-licensed Rituxan and 146-148 kDa for EU-approved MabThera. The HMW_a molecular masses observed were 281.7 kDa for ABP 798 (range: 228-337 kDa), 229.0 kDa for US-licensed Rituxan (range: 192-302 kDa), and 238.8 kDa for EU-approved MabThera (range: 178-271 kDa). The HMW_b molecular masses observed were 322.9 kDa for ABP 798 (range: 298-342 kDa), 325.8 kDa for US-licensed Rituxan (range: 293-371 kDa), and 330.9 kDa for EU-approved MabThera (range: 295-352 kDa). The HMW_c molecular masses observed were 411.2 kDa for ABP 798 (range: 336-463 kDa), 364.9 kDa for US-licensed Rituxan (range: 312-445 kDa), and 377.8 kDa for EU-approved MabThera (range: 314-408 kDa).

Assessor comment: *The SE-HPLC-SLS chromatograms are consistent with the SE-UHPLC chromatograms, with respect to the relative retention times for the HMW species detected.*

HMW species characterization

One lot each for ABP 798 (DS lot # 0010318855, used to fill the DP lot # 0010324182), US-licensed Rituxan (lot # 3712852) and EU-approved MabThera (lot # 3712852) were separated by size exclusion chromatography to obtain the HMW-enriched or main peak- enriched fractions for further characterization (Table 13). The US and EU fractions contain 87.7-89.0% HMW, 10.7% main and 0.2-1.6% LMW, while the ABP fraction contains 62.4% HMW, 37.4% main and 0.2% LMW. The characterization data of the enriched HMW fractions are provided in tabular and graphical formats as described as follows.

Assessor comment: *The ABP 798 DS lot used is representative of the clinical DP lot which showed the highest % HMW by SE-UHPLC. The enriched fractions of ABP 798 have significantly lower HMW and main species compared to that of the enriched US and EU fractions.*

Molecular mass by SE-HPLC-SLS: The chromatograms show that the HMW peak of ABP 798 predominantly consists of HMW_b species with a new shoulder peak, and that the HMW peaks of the US and EU lots consist of primarily HMW_c with minor levels of HMW_a and higher order aggregates (Figure 65). The observed molecular masses for the monomer peak are 144 kDa for ABP 798, 162 kDa for US-licensed Rituxan, and 152 kDa for EU-approved MabThera (Table 14). The molecular masses of HMW_a and HMW_c are not detected in the ABP 798 lots, and the molecular mass of HMW_b is not detected in the US and EU lots. It is stated that HMW_a peaks consist of a monomer associated with LMW species, that HMW_b peaks corresponds to a dimer, and that HMW_c peaks consist of a dimer mixed with higher order aggregates.

Assessor comment: *The SE-HPLC-SLS results of the enriched HMW species for fractionated ABP 798, US-licensed Rituxan and EU-approved MabThera appeared inconsistent with the results of the unfractionated samples, which show molecular mass data for all three HMW species. The HMW species identified by SE-HPLC-SLS and SE-UHPLC results (HMW_a, HMW_b and HMW_c) are also inconsistent with the HMW species identified from the ABP 798 DS characterization studies (HMW 1 and HMW 2; see Figure 29, Section S.3.1). Additionally,*

the chromatograms of the enriched HMW fractions showed new peaks that were not detected in the unfractionated ABP 798, US-licensed Rituxan, and EU-approved MabThera samples, i.e., the uncharacterized peak eluted at approximately 13 minutes for ABP 798, the “higher order aggregate” peak eluted at approximately 11 minutes for the US and EU lots. Amgen was requested to clarify the observed inconsistencies in the HMW species and putative structures in ABP 798, US-licensed Rituxan, and EU-approved MabThera (IR-3). It was clarified that the HMW_a, HMW_b, and HMW_c species are identified in fractionated and unfractionated samples of ABP 798, US-licensed Rituxan, and EU-approved MabThera, and the new peak observed for the fractionated ABP 798 sample is identified as dimer plus LMW species (pages 8-9, response to IR-3, SDN 8). The additional information and data provided are described below.

Information and data provided in the response to IR-3: The initial analysis did not report minor molecular masses which was the reason for the identified discrepancy between the data in Table 14 and Table 4. Amgen re-analyzed the results of the SE-HPLC-SLS chromatograms of the HMW-enriched fractions of ABP 798, US-licensed Rituxan, and EU-approved MabThera to include data for all HMW species variants and the results show the molecular mass values of 220-254 kDa for HMW_a, 283-303 kDa for HMW_b and 295-330 kDa for HMW_c (Figure 1 and Table 1). The fraction breakdown of the SE-UHPLC profile of ABP 798 shows that the HMW-enriched fraction consists of HMW1 and HMW2 fractions, in which the peak intensity of the HMW2 fraction is much lower than that of the HMW1 fraction (Figure 2 and Table 6).

The HMW1 fraction of ABP 798 (by SE-UHPLC) corresponds to the three dimer structures (HMW_a, HMW_b, and HMW_c) and “dimer plus LMW species” (i.e., the new peak detected in the HMW-enriched fraction of ABP 798).

The HMW2 fraction (by SE-UHPLC) is expected to contain the trimer and higher order aggregates based on the ABP 798 DS characterization results (see page 84, Section S.3.1). The presence of the trimer is not detected in the HMW-enriched fractions (i.e., combined HMW1 and HMW2 fractions) for all three products. The level of higher order aggregates (eluted at 11.2 minutes) in HMW-enriched fraction of ABP 798 is much lower than those in the US and EU lots.

Assessor comment: *The information provided support that the same dimeric species are detected in ABP 798, US-licensed Rituxan, and EU-approved MabThera regardless of fractionation. The breakdown of the HMW1 and HMW2 fractions by SE-UHPLC was not provided for the US and EU lots. However, the SE-UHPLC chromatograms provided indicate that HMW species are also present in the projected HMW2 fractions of the US and EU lots, based on retention time and peak intensity. The SE-UHPLC characterization data for ABP 798 DS indicate that the amount of the HMW2 fraction is very low compared to the HMW1 fraction, which is likely the reason why the presence of trimer and higher order aggregates was not detected in ABP 798 batches in the CAA, where the fractionated data were a result of analysis of the combined HMW1 and HMW2 fraction. The levels of the dimer plus LMW species detected in fractionated ABP 798 and the higher order aggregates in fractionated US-licensed Rituxan and EU-approved MabThera are low and thus not expected to have a significant impact on biological activity of these products.*

Evaluation of fractionated HMW species (structure-function studies):

Covalent linkages of HMW species by denatured SE-UHPLC (dSE-UHPLC): The dSE-UHPLC chromatograms of the HMW-enriched fraction of the ABP 798 lot are similar to those of the US and EU lots (Figures 66-67). All products are determined to contain approximately 30% (25-35%) of covalently linked HMW species (Table 15).

CDC activity: The relative potency of the HMW-enriched ABP 798 fraction (139%) is higher than the results of the US (73%) and EU (86%) lots, while the main peak-enriched fractions from each product show similar CDC activity of 96-102% (Table 16).

CD20 binding: The relative potency of the HMW-enriched ABP 798 fraction (72%) is higher than the results of the US (41%) and EU (43%) lots, while the main peak-enriched fractions from each product show similar CD20 binding activity of 96-98% (Table 17).

NK92 ADCC: The relative potency of the HMW-enriched ABP 798 fraction (79%) is higher than the results of the US (60%) and EU (57%) lots, while the main peak-enriched fraction from each product show similar NK92 ADCC activity of 79-88% (Table 18).

Assessor comment: *The HMW-enriched ABP 798 fraction shows increased potency for CDC ($\geq 66\%$ higher), CD20 binding ($\geq 31\%$ higher), and ADCC ($\geq 31\%$ higher) compared to the US and EU results. Considering that total % HMW content of the enriched ABP 798 fraction is significantly lower ($\geq 25\%$ lower) than the US and EU fractions, it was unclear if the increased potency detected in the HMW species fraction in ABP 798 could impact safety of ABP 798 and support a demonstration of highly similar between ABP 798, US-licensed Rituxan, and EU-approved MabThera. Amgen was requested to provide additional data and information to justify the observed differences in potency of the HMW species in ABP 798 (IR-3). The response to IR-3 (SDN 8) is summarized as the following.*

Information and data provided in the response to IR-3: A risk assessment for the potential impact of the observed differences in the HMW species between ABP 798, US-licensed Rituxan, and EU-approved MabThera was performed. The differences in relative potency were divided by the differences in % HMW between the HMW-enriched and main peak-enriched samples to estimate the change in relative potency by every 1% HMW species. The estimated relative potency at the worst-case (i.e., the upper limit of 4.2% HMW, per ABP 798 DP stability specification) was compared to that of the product containing no HMW species. For every 1% increase in the HMW level, the relative CDC potency values are expected to increase by 0.7% for ABP 798, and decrease by 0.2% for US-licensed Rituxan and 0.3% for EU-approved MabThera (Table 3). This results in a difference in relative CDC potency of +2.9% for ABP 798, -1.3% for US-approved Rituxan, and -0.8% for EU-approved MabThera, when the HMW level is increased from 0.0% to 4.2%. For every 1% increase in the HMW level, the relative NK92 ADCC potency values are expected to show a 0.1% decrease for ABP 798, a 0.2% decrease for US-licensed Rituxan, and a 0.3% decrease for EU-approved MabThera (Table 4). This results in a difference in relative NK92 ADCC potency of -0.4% for ABP 798, -0.8% for US-approved Rituxan, and -1.3% for EU-approved MabThera, when the HMW level is increased from 0.0% to 4.2%. For every 1% increase in the HMW level, the relative CD20 binding potency values are expected to show a 0.4% decrease for ABP 798, a 0.7% decrease for US-licensed Rituxan, and a 0.6% decrease for EU-approved MabThera (Table 5). This results in a difference in relative CD20 binding potency of -1.7% for ABP 798, -2.9% for US-approved Rituxan, and -2.5% for EU-approved MabThera, when the HMW level is increased from 0.0% to 4.2%.

Assessor comment: *The estimated relative CDC potency values when the product contains the maximally allowed HMW species level of 4.2% are consistent between the three products (i.e., 100% for ABP 798, 95% for US-licensed Rituxan, and 101% for EU-approved MabThera). Likewise, the estimated relative potency values for NK92 ADCC (i.e., 87% for ABP, 78% for US-licensed Rituxan, and 81% for EU-approved MabThera) and CD20 binding (i.e., 95% for ABP and US-licensed Rituxan and 94% for EU-approved MabThera) are consistent between the three products. Based on the totality of the data and information provided, the observed differences in the HMW species do not preclude a demonstration of highly similar and support establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Size-related purity and impurities under reduced conditions by rCE-SDS

Method description and validation summary: The levels of the reduced antibody (HC + LC), fragments (LMW + median molecular weight or MMW), and NGHC in the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) are assessed using the release testing method by rCE-SDS (see method description in Section P.5.2). The method was validated at ADL for release testing (see Section P.5.3). The method was also qualified for use at the ATO AS, AWA, and AMA sites and transferred from the ATO AS to ATO QC sites. The

method transfer was stated to be waived per USP <1224>, based on the experience of the ATO QC site with the rCE-SDS method (Table 7 and page 19, response to IR-3, SDN 8). The method qualification results for the ATO AS, AWA, and AMA sites show repeatability CV of 0.1% for the pre-peaks and main peaks for all sites and intermediate CV of 0.4% for ATO AS and 0.1% for AMA and AWA (Table 20, response to IR-3, SDN 8).

Assessor comment: See Section P.5.3 regarding the adequacy of the method validation results for the rCE-SDS method for testing of ABP 798. Additionally, the rCE-SDS electropherograms of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results also support suitability of the rCE-SDS method for the intended purpose. The method validation and qualification results provided support consistent performance between the ADL, ATO AS, AMA, and AWA sites. However, we do not agree with the waiver justification to support not performing method transfer studies to support performance of a non-compendial method at the ATO QC testing site. Amgen was requested to provide additional information and data to support that the nrCE-SDS method is appropriately validated at the ATO QC site (IR-4). In response to IR-4, Amgen provided the following information and data.

Information and data provided in the response to IR-4, SDN 9: The trend charts of the PRS at ATO AS and ATO QC were provided (Figure 4). The % LC+HC results are $98.2 \pm 0.2\%$ for ATO AS and $98.2 \pm 0.1\%$ for ATO QC.

Assessor comment: The trend charts of the PRS are sufficient to support consistent method performance at ATO AS and ATO QC.

CAA lots and test results: The total independent ABP 798 lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera. The rCE-SDS profiles of 9 lots each of the three products were also assessed in three side-by-side comparisons. Data were generated at the ATO AS, ATO QC, AMA, AWA, and ADL sites. The electropherograms of ABP 798, US-licensed Rituxan and EU-approved MabThera show similar distribution of the HC, LC, LMW, MMW, and NGHC peaks, with respect to retention time and peak shape (Figures 16-18). The % HC+LC, % LMW+MMW and % NHGC data of the ABP 798, US and EU lots show up to 2%, 1.5%, and <0.5% variability across material ages, respectively (Figures 19-21). The non-adjusted (i.e., initial time point) and age-adjusted data for % HC+LC and % LMW+MMW as well as non-adjusted data for % NGHC are provided in tabulated and graphic formats. The non-adjusted and age-adjusted results of the two ABP lots aged 36 months and three US and two EU lots aged 30 months are consistent, and the linear regression parameter estimates (i.e., product-specific slope, lot-specific intercept) and plots are also provided (Tables 23 and 26-27 and Figures 70-71).

The non-adjusted % HC+LC results are 97.8-98.4% for ABP 798, 97.2-98.9% for US-licensed Rituxan, and 97.8-98.7% for EU-approved MabThera (Table 33). The non-adjusted % LMW+MMW results are 0.0-0.6% for ABP 798, 0.1-1.4% for US-licensed Rituxan, and 0.1-1.1% for EU-approved MabThera (Table 34). The non-adjusted % NGHC results are 0.5-0.6% for ABP 798, 0.4-0.5% for US-licensed Rituxan, and 0.4-0.6% for EU-approved MabThera (Table 7). All ABP 798 lots are within the US-based QRs of 97.32-99.41% HC+LC and 0.00-1.22% LMW+MMW as well as the EU-based QRs of 97.60-98.98% HC+LC and 0.00-1.17% LMW+MMW (Figures 85-88). The % NGHC results of all ABP 798 lots are outside of US-based QR and slightly higher (up to 0.07% differences) than the upper end of the US-based QR of 0.29-0.53% (Figure 27), and 8 of the 14 ABP 798 lots (57%) are within the EU-based QR of 0.26-0.59% (Figure 30). All EU lots are also within the US-based QRs for % HC+LC and % LMW+MMW (Figures 89-90), and 27 of the 30 EU lots (90%) are within the US-based QR (Figure 33).

The age-adjusted % HC+LC results are 97.0-97.7% for ABP 798, 97.3-98.4% for US-licensed Rituxan, and 97.2-98.2% for EU-approved MabThera (Table 5). The age-adjusted % LMW+MMW results are 0.6-1.2% for ABP 798 and EU-approved MabThera and 0.5-1.3% for US-licensed MabThera (Table 6). For % HC+LC, 5 of the 14 (36%) ABP 798 lots are within the US-based QR of 97.38-98.65% (Figure 25), and 12 of the 14 (86%) ABP 798 lots are within the EU-based QR of 97.08-98.50% (Figure 28). For % LMW+MMW, all ABP 798 lots are within

the US-based QR of 0.27-1.20% and the EU-based QR of 0.33-1.32% (Figures 26 and 29). Twenty-eight of the 30 (93%) EU lots are within the US-based QR for % HC+LC (Figure 31), and all EU lots are within the US-based QR for % LMW+MMW (Figure 32). The ABP 798 outliers identified include two clinical lots with up to 0.38% lower HC+LC content, four PV lots with up to 0.08% lower HC+LC content, and three development lots with up to 0.38% lower HC+LC content, when compared to the lower end of the US-based QR.

Assessor comment: *The observed differences in the non-adjusted and age-adjusted %HC+LC results (<0.4% differences) and non-adjusted % NGHC results (<0.1% differences) are minor. Although the NGHC content of an IgG can have an impact on ADCC activity, no significant change in ADCC activity was observed between the three rituximab products. Therefore, the rCE-SDS test results do not preclude a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Size-related purity and impurities under non-reduced conditions by nrCE-SDS

Method description and validation summary: The levels of the main peak and pre-peaks were assessed using the in-process testing by nrCE-SDS method (see method description in Section S.4.2). The method was validated at the ADL site for in-process testing during ABP 798 DS manufacture (see Section S.4.3). The method was also qualified for use at the ATO AS, ATO QC, AMA, and AWA testing sites. The method qualification results for the ATO AS, AMA, and AWA sites show a repeatability CV of 0.1% for the pre-peaks and main peak for all sites and an intermediate precision CV of 0.4% for ATO AS and 0.1% for AMA and AWA (Table 20, response to IR-3, SDN 8). The method transfer report from the ATO Product and Process Development (ATO P&PD) to ATO QC sites show a repeatability CV of 0.1% for the main peak, 2.3% for the total pre-peaks > limit of quantification (LOQ) and 0.0% for the total post-peaks > LOQ and intermediate CV of 0.4% for the main peak, 13.3% for the total pre-peaks > LOQ and 0.0% for the total post-peaks > LOQ (Table Section 3A, Report # RPT-491257, SDN 8). The method transfer was performed in two runs of three independent preparations each by one analyst in the receiving laboratory, and the results were compared to the results generated by the sending laboratory using the same experimental design.

Assessor comment: *See Section S.4.3 regarding the adequacy of the method validation results of the nrCE-SDS method for testing of ABP 798 at ADL. Additionally, the nrCE-SDS electropherograms of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results below also support suitability of the nrCE-SDS method for the intended purpose. The method validation, qualification, and transfer information and data provided support consistent method performance across all testing sites.*

CAA lots and test results: The total independent ABP 798 lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera. The nrCE-SDS profiles of 9 lots each of the three products were also assessed in three side-by-side comparisons. Data were generated at the ATO AS, ATO QC, AMA, AWA, and ADL sites. The electropherograms of ABP 798, US-licensed Rituxan, and EU-approved MabThera show similar distribution of the main and pre-peaks (Figures 34-36). The % main and % pre-peaks by nrCE-SDS results appear consistent regardless of material age (Figures 37-38). The non-adjusted % main results were 95.9-98.8% for ABP 798, 96.3-97.6% for US-licensed Rituxan, and 96.8-97.7% for EU-approved MabThera (Table 8 and Figure 39). The non-adjusted % pre-peaks results are 1.2-4.1% for ABP 798, 2.4-3.7% for US-licensed Rituxan, and 2.3-3.2% for EU-approved MabThera (Table 9 and Figure 40). For % main, 4 of the 14 (29%) ABP 798 lots are within the US-based QR of 96.34-97.90% (Figure 41) and the EU-based QR of 96.48-97.80% (Figure 43). For % pre-peaks, 4 of the 14 (29%) ABP 798 lots are within the US-based QR of 2.10-3.65% (Figure 42) and the EU-based QR of 2.20-3.52% (Figure 44). All EU lots are within the US-based QRs for % main and % pre-peaks (Figures 45-46). The ABP 798 outliers identified include one clinical lot with 0.25% higher pre-peaks content and one development lot with 0.45% higher pre-peaks content compared to the upper bound of the US-based QR; and four PV lots with up to 0.6% lower pre-peaks content and four development lots with up to 0.9% lower pre-peaks content compared to the lower bound of the US-based QR. These are the same ABP 798 outliers with differences for % main.

Assessor comment: The observed differences in % pre-peaks (<1.0% differences) and % main (<1.0% differences) are minor. As the characterization results show no impact on CDC and ADCC activities of ABP 798 in the presence of up to 47.7% pre-peaks (see Tables 77 and 80, Section S.3.2) and the CAA results for potency and biological activity show no significant differences, the observed differences in % pre-peaks and % main by nrCE-SDS do not appear to have an impact on potency. Therefore, the nrCE-SDS test results do not preclude a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

Charge heterogeneity by CEX-HPLC

Method description and validation summary: The main, acidic and basic charge species are assessed using the release test by CEX-HPLC method (see method description in Section P.5.2). The method was validated at the ADL site for release testing of ABP 798 DP (see Section P.5.3). The method was also qualified for use at the ATO AS, ATO QC, AMA, and AWA testing sites. The method qualification results for the ATO AS, AMA, and AWA sites show repeatability CVs of 0.1-0.5% for the acidic peaks, 0.1-0.4% for the main peak and 0.1-0.3% for the basic peaks and intermediate CVs of 0.2-0.4% for the acidic peaks, 0.2-0.5% for the main peak, and 0.2-0.5% for the basic peaks (Table 21, response to IR-3, SDN 8). The method transfer results from the ATO P&PD to ATO QC sites show a repeatability CV of 0.126% and an intermediate precision CV of 0.211% for the main peak (Table Section 3A, Report # RPT-491205). The method transfer was performed in two runs of three independent preparations each of the DS samples at 100% load by one analyst using two instruments at the receiving laboratory, and the results were compared to the data generated by the sending laboratory using the same experimental design.

Assessor comment: See Section P.5.3 regarding the adequacy of the method validation results of the CEX-HPLC method for testing of ABP 798. The electropherograms provided as part of the CAA results support suitability of the CEX-HPLC method for evaluation of charge variants in ABP 798, US-licensed Rituxan, and EU-approved MabThera. Limited information was provided in the method transfer report for the ATO QC site, however, the following CVs were calculated independently by the assessor based on the raw data provided: the repeatability CVs of 0.2% for the main and acidic peaks and 0.7% for the basic peaks, the intermediate precision CVs of 0.4% for the main peak, 1.0% for the acidic peaks and 0.6% for the basic peaks, and the reproducibility CVs of 0.3% for the main peak, 1.0% for the acidic peaks and 2.0% for the basic peaks are calculated by the assessor. Overall, the method validation, qualification, and transfer information and data provided support consistent method performance across all testing sites.

CAA lots and test results: The total independent ABP 798 lots were evaluated against the total lots of US-licensed Rituxan and EU-approved MabThera. The CEX-HPLC profiles of 9 lots each of the three products were also assessed in three side-by-side comparisons. Data were generated at the ATO AS, ATO QC, ADL, AMA, and AWA sites. The chromatograms of ABP 798, US-licensed Rituxan and EU-approved MabThera show similar distribution of the main, acidic, and basic peaks with respect to relative retention times (Figures 47-49). The % acidic, % main and % basic data of the ABP 798, US and EU lots show up to 8%, 10%, and 2% variability over material ages (Figures 50-52). The non-adjusted (i.e., initial time point) and age-adjusted data for % acidic, % main and % basic are provided in tabulated and graphic formats. The non-adjusted and age-adjusted results of the three ABP lots aged 36 months and two US and three EU lots aged 30 months are consistent, and the linear regression parameter estimates (i.e., product-specific slope, lot-specific intercept) and plots are also provided (Tables 23 and 28-30 and Figures 72-74).

The non-adjusted % acidic results are 16.8-19.6% for ABP 798, 17.4-22.4% for US-licensed Rituxan, and 16.3-22.7% for EU-approved MabThera (Table 35 and Figure 91). The non-adjusted % main results are 72.3-74.4% for ABP 798, 64.4-73.5% for US-licensed Rituxan, and 65.8-73.9 for EU-approved MabThera (Table 36 and Figure 92). The non-adjusted % basic results are 7.7-9.2% for ABP 798, 8.4-14.6% for US-licensed Rituxan, and 9.5-13.1 for EU-approved MabThera (Table 37 and Figure 93). All ABP 798 lots are within the US-based QRs of

15.81-23.94% for the acidic peaks, 62.18-75.48% for the main peak, and 7.04-15.55% for the basic peaks (Figures 94-96). All ABP 798 lots are within the EU-based QR of 16.03-24.86% for the acidic peaks, and 12 of the 14 ABP 798 lots (86%) are within the EU-based QRs of 63.32-74.11% for the main peak and 8.07-13.61% for the basic peaks (Figures 97-99). All EU lots are also within the US-based QRs for the acidic, main, and basic peaks (Figures 100-102).

The age-adjusted % acidic results are 20.6-24.6% for ABP 798, 19.9-23.8% for US-licensed Rituxan, and 20.3-24.4% for EU-approved MabThera (Table 10 and Figure 53). The age-adjusted % main results are 67.3-71.2% for ABP 798, 64.6-71.4% for US-licensed Rituxan, and 64.8-70.3% for EU-approved MabThera (Table 11 and Figure 54). The age-adjusted % basic results are 7.8-9.2% for ABP 798, 6.9-12.6% for US-licensed Rituxan, and 8.6-12.2% for EU-approved MabThera (Table 12 and Figure 55). For the acidic peaks, all ABP 798 lots are within the US-based QR of 18.88-25.22% (Figure 56) and the EU-based QR of 19.49-25.68% (Figure 59). For the main peak, all ABP 798 lots are within the US-based QR of 62.36-73.77% (Figure 57), and 13 of the 14 (93%) ABP 798 lots are within the EU-based QR of 63.67-71.14% (Figure 60). For the basic peaks, all ABP 798 lots are within the US-based QR of 5.78-14.98% (Figure 58) and the EU-based QR of 7.60-12.42% (Figure 61). All EU lots are within the US-based QRs for the acidic, main, and basic peaks (Figures 62-64). The ABP 798 outlier is a development lot with up to 0.06% higher main peak area.

Assessor comment: *The non-adjusted and age-adjusted CEX-HPLC results for charge heterogeneity support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Charge variants characterization

One lot each for ABP 798 (DS lot # 0010318855), US-licensed Rituxan, and EU-approved MabThera were separated using CEX-HPLC to prepare fractions enriched with the main, acidic, or basic species (Table 19). The acidic peaks-enriched fraction contents are 84% for the ABP 798 and EU lots and 74% for the US lot. The main peak-enriched fraction contents are 99-100% for the ABP 798 and EU lots and 91% for the US lot. The basic peak-enriched fraction contents are 83% for the ABP 798 lot, 90% for the US lot, and 100% for the EU lot. The reduced and alkylated tryptic peptide mapping analysis shows that ABP 798, US-licensed Rituxan and EU-approved MabThera have similar post-translational modifications profiles, i.e., deamidated Asn388 and Asn393 for the acidic peak-enriched fractions, C-terminal Lys451 and N-terminal Glu1 for the basic peaks-enriched fractions (Table 20). The C-terminal Lys451 levels of the basic peak-enriched fractions are higher in (30%) the ABP 798 compared to 5% for US-licensed Rituxan, and 9% for EU-approved MabThera. The fractionated and unfractionated samples of the ABP 798, US and EU lots contained 1-5% Trp 106 oxidation, ≤1% Met 34 oxidation, 3-6% Met 256 oxidation, 1-5% Met 432 oxidation. The CDC bioassay results for the acidic peaks-enriched fractions (relative potency: 103% for ABP 798 and 107-112% for US and EU lots), main peak-enriched fractions (107% for ABP 798 and 118-128% for US and EU lots), basic peaks-enriched fractions (92% for ABP 798 and 81-87% for US and EU lots), and unfractionated materials (105% for ABP 798 and 107-111% for US and EU lots) are provided (Table 21). The NK92 ADCC assay results for the acidic peaks-enriched fractions (70% for ABP 798 and 57-60% for US and EU lots), main peak-enriched fractions (85% for ABP 798 and 73-80% for US and EU lots), basic peaks-enriched fractions (97% for ABP 798 and 73-76% for US and EU lots), and unfractionated materials (84% for ABP 798 and 66-78% for US and EU lots) are also provided (Table 22).

Assessment comment: *The difference in C-terminal lysine observed between ABP 798 and US and EU lots is not a concern considering the removal of C-terminal lysine of IgG products upon intravenous administration. Further, the peptide mapping results of c-terminal lysine content in unfractionated antibody showed similar amounts among the three products. The characterization results of the charge variants fractions support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Subvisible Particles, Submicron Particles and Aggregates (Document entitled “Comparative analytical Assessment – Particles and Aggregates”)

Subvisible particles by HIAC

Method description and qualification summary: The HIAC method detects SVPs of $\geq 2 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$ particle sizes in the test article in accordance of USP <787>. The method was verified at ATO AS (Table 4, response to IR-4, SDN 9) and ADL (see Sections P.5.2 and P.5.3; RPT-513689, Section 1.11.1, SDN 9) and transferred from ATO AS to ATO QC. The ATO AS method shows no interference from filtered sample matrix and larger particles for a given size (e.g., $5 \mu\text{m}$ from $15 \mu\text{m}$ particles, $10 \mu\text{m}$ from $30 \mu\text{m}$ particles), up to 9.8% CV for repeatability, up to 22.4% CV for intermediate precision, within target counts of the particle count standards for accuracy, and R^2 of >0.96 for linearity over the ranges evaluated. A method waiver for the same method performed at ATO QC was stated to be claimed per USP <1224>, based on the experience of the site with the method (page 17, response to IR-4, SDN 9).

Assessor comment: The method validation and qualification results support suitability of the HIAC method at ADL and ATO AS. While method verification/transfer data were not provided to support method performance at ATO QC for the CAA results, the data are consistent across testing sites. Further, SVP counts are not expected to be evaluated as part of the CAA to support the analytical portion of the scientific bridge, and further information and data will be assessed to enable proper control over this product quality attribute as part of the ABP 798 manufacturing process control strategy.

CAA lots and test results: The total of 26 ABP 798 DP lots were assessed against 22 US-licensed Rituxan and 21 EU-approved MabThera lots (based on availability at the time of testing). Data were generated at the ATO AS, ATO QC, and ADL sites. For each SVP size evaluated (i.e., $\geq 2 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, $\geq 25 \mu\text{m}$), all ABP 798 lots are visually within the data ranges of the US lots and of the EU lots (Figures 1-4 and Tables 1-4).

Subvisible particles by MFI

Method description and qualification summary: The MFI method detects total and non-spherical particles of $\geq 5 \mu\text{m}$ size in the sample solution. The MFI method qualification results show no assay interference from the reconstitution diluent (specificity) and repeatability CV of 19.3% at the ATO AS site with 207 ± 40 particles/mL and 13.7% at the (b) (4) site with 539 ± 74 particles/mL for total $\geq 5 \mu\text{m}$ SVP; and 23.2% at the ATO AS site with 177 ± 41 particles/mL and 14.4% at the (b) (4) site with 507 ± 73 particles/mL for non-spherical $\geq 5 \mu\text{m}$ SVP (Table 15, response to IR-3, SDN 8).

Assessor comment: The method qualification summary provided supports consistent method performance across all testing sites for total and non-spherical SVPs sized $\geq 5 \mu\text{m}$.

CAA lots and test results: The total 26 ABP 798 DP lots were assessed against 22 US-licensed Rituxan and 21 EU-approved MabThera lots (based on availability at the time of testing). Data were generated at the ATO AS and Elion sites. For total $\geq 5 \mu\text{m}$ particles, all ABP 798 lots are visually within the data range of the US- and EU-lots (Figure 5 and Table 5). For $\geq 5 \mu\text{m}$ non-spherical particle counts, 21 of the 26 (81%) ABP 798 lots have counts within the US-based QR of 0-248 particles/mL, and 20 of the 26 (77%) ABP 798 lots have counts within the EU-based QR of 0-71 particles/mL, and all EU lots are within the US-based QR (Figures 6-9 and Table 6). The ABP 798 outliers for the $\geq 5 \mu\text{m}$ non-spherical particle test results include one clinical lot # 0010327844 (total: 312 particles/mL; non-spherical: 258 particles/mL) and two development (b) (4) lots # 6357 0911_7L902 (total: 612 particles/mL; non-spherical: 508 particles/mL) and # 6357 0950_7L902 (total: 254 particles/mL; non-spherical: 178 particles/mL).

Assessor comment for SVP by HIAC and MFI methods: The same ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were used to generate the CAA results by HIAC and MFI. The comparison of the counts

of the total and non-spherical particles sized $\geq 5 \mu\text{m}$ shows that the ABP 798 lots containing higher amounts of non-spherical particles are also the lots with a higher ratio of non-spherical versus total particles. Nevertheless, the comparative analysis data show that only five out of 26 ABP 798 lots were out of the QR for the non-spherical particles, which is likely practically insignificant considering method variability and number of lots assessed. SVP monitoring and control will be evaluated as part of the overall ABP 798 manufacturing control strategy.

Submicron particles by field flow fractionation (FFF)

Method description and qualification summary: Submicron particles in the test samples were fractionated and characterized using FFF, and the results were compared to the data from polystyrene particle standards of 100, 200, and 500 nm sizes (positive control) and formulation buffer blank (negative control). The FFF qualification results showed clear separation of rituximab from the particle standards and visually similar profiles across the three ABP 798 lots evaluated (Table 24, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”).

Assessor comment: The method qualification summary and the FFF profiles of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results below support suitability of the FFF method for the intended purpose.

CAA lots and test results: Six lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were assessed side-by-side. Data were generated at the ATO site. The FFF size distribution profiles of the ABP 798, US and EU lots show a single peak corresponding to the monomer (Figures 10-11).

Submicron particles by dynamic light scattering (DLS)

Method description and qualification summary: The DLS method measures submicron particle size distribution in the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera). The DLS qualification results for the DLS method showed that baseline resolution of the test article from the particle standard, with $<10\%$ RSD for ABP 798 (Table 25, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”).

Assessor comment: The method qualification summary and the DLS profiles of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results below support suitability of the DLS method for the intended purpose.

CAA lots and test results: Six lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were assessed side-by-side. Data were generated at the ATO site. The DLS size distribution profiles of the ABP 798, US and EU lots show a single peak corresponding to the monomer (Figures 12-13).

Assessor comment for submicron particles by FFF and DLS methods: The same ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were used to generate the CAA results by FFF and DLS. The submicron particle counts are supportive of a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

Aggregates by sedimentation velocity-analytical ultracentrifugation (SV-AUC)

Method description and qualification summary: The SV-AUC method measures the levels of the monomer and HMW species in the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera). The method was qualified at the ATO AS and (b) (4) testing sites, using ABP 798 and an IgG2 antibody, respectively (page 7, response to IR-4, SDN 9). The SV-AUC qualification summaries show baseline separation for close sedimentation coefficients (Svedberg unit, S) at (b) (4) (specificity), intermediate precision of 0.013 S for monomer at both sites, 0.0581 S for HMW species at (b) (4), and 0.377 S for HMW species at ATO AS, and the LOQ of 3.7% for HMW species at (b) (4) (Table 26, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”; Table 16, response to IR-3, SDN 8).

Assessor comment: Both the IgG2 antibody and ABP 798 are monoclonal antibodies with presence of HMW species, thus the IgG2 antibody is representative of ABP 798 for SV-AUC analysis of HMW species. The sedimentation coefficient distribution profiles of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support suitability of the SV-AUC method for these products. The method qualification information and data provided support consistent method performance across all testing sites.

CAA lots and test results: Nine lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were assessed side-by-side. Data were generated at the ATO and (b) (4) sites. The sedimentation coefficient distribution profiles of ABP 798 are consistent to those of the US and EU lots (Figures 14-15). The HMW levels in all lots are below the LOQ for all three products. For the monomer levels, all ABP 798 lots are within the US-based QR of 94.18-100.00% and the EU-based QR of 93.02-100.0% (Figures 16-18 and Table 7). All EU lots are also within the US-based QR (Figure 19).

Assessor comment: The monomer and HMW species by SV-AUC results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

Protein Concentration and Volume (Document entitled “Analytical Similarity Assessment – General Properties”)

Protein concentration

Method description and verification summary: Protein concentration of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is determined in accordance of USP <857>. The method was validated at ADL (co-validated at ARI) and then transferred to (b) (4) (see Sections P.5.2 and P.5.3; Report # RPT-53323 and QK VB 38309e, Section 1.11.1, SDN 9). A method waiver for the method performed at ATO AS, ATO QC and AWA is stated to be claimed per USP <1224>, based on the experience of these sites with the method (page 17, response to IR-4, SDN 9).

Assessor comment: USP <857> describes an extensive set of guidelines and requirements for the performance verification of UV-Visible spectrophotometers. Amgen stated that the same method that was co-validated at ADL and ARI (see Section S.4.3) was used throughout development with no changes made and the same method used at all sites. The CAA results provided demonstrate consistent protein concentration evaluations across all sites. Overall, the method appears appropriate for its intended use.

CAA lots and test results: The total of 26 ABP 798 DP lots were assessed against the total lots of US-licensed Rituxan and EU-approved MabThera, in both 100 mg and 500 mg dose presentations. Data were generated at the ATO AS, ATO QC, AWA, ADL and (b) (4) sites. The protein concentrations values are 9.6-10.7 mg/mL for ABP 798 (i.e., 9.7-10.7 mg/mL for the 14 independent lots), 9.8-10.8 mg/mL for US-licensed Rituxan, and 9.8-10.7 mg/mL for EU-approved MabThera (Table 1 and Figure 1). Twenty-five of the 26 (96%) ABP 798 lots are within the US-based QR of 9.47-10.63 mg/mL and EU-based QR of 9.58-10.60 mg/mL (Figures 2-3). The protein concentration data of 97% (29/30) of the EU lots are also within the US-based QR (Figure 4). The ABP 798 outlier is a clinical lot with 0.07 mg/mL higher protein concentration than the upper bound of the US-based QR.

Assessor comment: The protein concentration results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan and EU-approved MabThera.

Extractable Volume

Method description and verification summary: Extractable volume of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is determined in accordance of USP <1>. Method verifications at the ATO AS

and ATO QC testing sites were stated to be waived per USP <1224>, based on the experience of these sites with this method (page 19, response to IR-4, SDN 9).

Assessor comment: *Method verification data were not provided to support method performance. However, considering this method is compendial and that the extractable volume results (total n=59) are consistent when generated across sites, the method appears sufficient for its intended purpose.*

CAA lots and test results: The total of 26 ABP 798 DP lots including 14 lots for 100 mg/vial and 12 lots for 500 mg/vial were assessed against the same dose presentations of the 19 US-licensed Rituxan lots and the 14 EU-approved MabThera lots (based on availability at the time of testing). Data were generated at the ATO AS and ATO QC testing sites. The 100 mg lots have extractable volume of 10.1-10.4 mL for ABP 798, 10.1-10.4 mL for US-licensed Rituxan, and 10.1-10.3 mL for EU-approved MabThera (Figure 5 and Table 2). The 500 mg lots have extractable volume of 50.2-50.9 mL for ABP 798, 50.5-50.8 mL for US-licensed Rituxan, and 50.5-50.8 mL for EU-approved MabThera (Figure 6 and Table 3). There are 3 500 mg/vial ABP 798 lots containing less than 50.5 mL per vial # ABP 0010373733, ABP 0010373734 and ABP 0010373735, which were determined to have extractable volume of 50.4 mL, 50.2 mL and 50.4 mL, respectively.

Assessor comment: *The extractable volume results are consistent across all lots of the three products and provide additional supporting evidence that ABP 798 will be able to meet its proposed label claim which is the same as that for US-licensed Rituxan.*

Primary Structure (Document entitled “Analytical Similarity Assessment – Primary Structure”)

Intact molecular mass by mass spectrometry

Method description and qualification summary: The intact molecular mass of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is determined using reverse-phase ultra-high performance liquid chromatography (RP-UHPLC) coupled with electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) and compared to the theoretical mass based on the amino acid sequence of rituximab. The method verification result shows that the measured mass of ABP 798 is within instrument capability of ± 100 ppm of the theoretical mass (Table 14, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”).

Assessor comment: *The method qualification summary provided and the deconvoluted mass profiles of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support the suitability of the intact molecular mass by ESI-TOF-MS method for the intended purpose.*

CAA lots and test results: Six lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were side-by-side assessed. The deconvoluted mass profiles of ABP 798, US-licensed Rituxan, and EU-approved MabThera show four major peaks corresponding to the intact antibody with A2G0F:A2G0F, A2G0F:A2G1F, A2G1F:A2G1F or A2G1F:A2G2F glycosylation as well as minor peaks (Figures 1-2). For all lots evaluated the differences between the observed and theoretical masses of the four peaks are within method accuracy (Tables 1-2).

Assessor comment: *The intact molecular mass by RP-UHPLC/ESI-TOF-MS results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera. See additional discussion on the HILIC glycan map section for the minor peaks observed.*

Reduced and deglycosylated mass by mass spectrometry

Method description and qualification summary: The test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is treated using peptide-N-glycosidase F (PNGase F), denatured, and reduced to yield

reduced and deglycosylated fragments. The resultant fragments are separated using RP-UHPLC and analyzed using ESI-TOF-MS. The method verification result shows that the measured mass of ABP 798 is within instrument capability of ± 100 ppm of the theoretical mass (Table 15, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”).

Assessor comment: *The method qualification summary provided and the deconvoluted mass profiles of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support the suitability of the reduced and deglycosylated molecular mass by ESI-TOF-MS method for the intended purpose.*

CAA lots and test results: Six lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were side-by-side assessed. The deconvoluted mass profiles of ABP 798, US-licensed Rituxan, and EU-approved MabThera show major peaks corresponding to HC and LC, two minor peaks for the LC fraction, and four minor peaks for the HC fraction (Figures 3-6). For all lots evaluated the differences between the observed and theoretical masses are within method accuracy (Tables 3-4).

Assessor comment: *The reduced and deglycosylated mass by RP-UHPLC/ESI-TOF-MS results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Amino acid sequence and PTMs by reduced peptide map

Method description and qualification summary: The trypsin-digested test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is analyzed using reduced peptide map on a RP-UHPLC system with UV215 detection and online ion trap mass spectrometry. The method was qualified at the ATO and AS testing sites for enzyme specificity (difference between the observed and theoretical masses: ≤ 5 ppm for ATO AS and ≤ 7 ppm for AMA), repeatability (relative peak height ratios: within 96-100% for ATO AS and within 97-102% for AMA), 80% protein recovery at AMA, and 0.001% carryover at AMA (Table 16, document entitled “Analytical Similarity Assessment – Methods Qualification Summary” plus Table 11, response to IR-3, SDN 8).

Assessor comment: *The method qualification summary provided and the tryptic peptide map chromatograms of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support the suitability of the amino acid sequence and PTMs by reduced peptide map method for the intended purpose. The additional information provided in the IR response also support consistent method performance across all testing sites.*

CAA lots and test results: Nine lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were side-by-side assessed. Data were generated at the ATO AS and AMA sites. The reduced peptide map profiles of ABP 798 are similar to those of US-licensed Rituxan and EU-approved MabThera, and no new peak is detected above the integrity limit (Figures 7-9). For all lots evaluated the differences between the observed and theoretical masses for the fragments, chemical modifications and post-translational modifications (e.g., % N-terminal pE1 of LC) are within method accuracy, ± 50 ppm of the theoretical masses (Tables 5-8).

Assessor comment: *The identical amino acid sequences and similar post-translation modification profile results by reduced peptide map support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Disulfide structure by non-reduced peptide map

Method description and qualification summary: The endoprotease Lys-C-digested test article (e.g. ABP 798, US-licensed Rituxan, EU-approved MabThera) is analyzed using non-reduced peptide map on a RP-UHPLC system with UV215 detection. The disulfide bond-containing peptide fragments (Figure 10) are identified by comparing the results from non-reduced and reduced peptide map data, and the molecular masses of these fragments were measured using ESI high-resolution mass spectrometry. The method was qualified for enzyme specificity (see

below), 88% protein recovery, and 0.2% carryover (Table 17, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”). The qualification results for specificity show that the observed masses of <8,000 Da peptides are up to 4.6 ppm different from the theoretical masses, and that the observed masses of >9,000 Da peptides are up to 70.4 ppm different from the theoretical masses.

Assessor comment: *The method qualification summary provided and the tryptic peptide map chromatograms of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support the suitability of the disulfide structure by non-reduced peptide map method for the intended purpose.*

CAA lots and test results: Two lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were side-by-side assessed. Data were generated at the ATO site. The non-reduced peptide map profiles of ABP 798 are similar to those of the US and EU lots, and no new peak is detected above the integrity limit (Figures 11-12). For most of the peptides evaluated, the differences between the observed and theoretical masses for the disulfide bond-containing peptide fragments, are within the method variability observed for masses of <8,000 Da or >9,000 Da (Tables 9-12). The other reduced disulfide-linked Lys-C peptide H21 (C325-K326) with a theoretical mass of 249.1 is not detected in all lots evaluated.

Assessor comment: *The absence of the peptide H21 (C325-K326), which has the smallest theoretical molecular mass among the target peptides, is likely due to method limitations for detection of small masses. Additionally, this peptide is consistently reported as “not detected” across the rituximab products assessed. Based on the totality of structural data provided, the disulfide bonds results are acceptable and do not preclude a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan and EU-approved MabThera.*

Glycan map by HILIC

Method description and qualification summary: The glycan map of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is characterized using the in-process testing by HILIC method (see method description in Section S.4.2). The method was validated at the ATO QC site for in-process testing during ABP 798 DS manufacture (see Section S.4.3). The method was also qualified for use at the ATO AS and AMA testing sites. The method qualification results for the ATO AS and AMA sites show repeatability standard deviations of up to 0.2% and intermediate precision standard deviations of up to 0.2% for afucosylation, high mannose, galactosylation, and total afucosylation (Table 12, response to IR-3, SDN 8).

Assessor comment: *See Section S.4.3 regarding the adequacy of the method validation result of the HILIC method. Additionally, the glycan maps of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support the suitability of the glycan map by HILIC method for the intended purpose. The method validation and qualification information and data provided support consistent method performance across all testing sites.*

CAA lots and test results: The total independent ABP 798 lots were evaluated against the total lots of US-licensed Rituxan and EU-approved MabThera lots. The glycan maps of 9 lots each of the three products were also assessed in three side-by-side comparisons. Data were generated at the ATO AS, ATO QC, and AMA sites. The chromatograms show visually similar distribution of glycoforms between the ABP 798, US and EU lots, with A2G0F, A2G1Fa, A2G1Fb and A2G2F being the most abundant glycoforms of >10% content (Figures 13-15 and Tables 13-15). The selected glycan group results for all lots are summarized as the following:

- **Total afucosylation:** 3.0-3.9% for ABP 798, 2.9-4.4% for US-licensed Rituxan, and 2.7-4.5% for EU-approved MabThera (Table 16 and Figure 16). The data of all ABP 798 lots are within the US-based QR of 2.4-4.8% and the EU-based QR of 2.2-4.9% (Figures 21 and Figure 25). The EU data are also within the US-based QR (Figure 29).
- **Afucosylation:** 1.6-2.3% for ABP 798, 1.1-2.6% for US-licensed Rituxan, and 1.3-2.5% for EU-approved MabThera (Table 17 and Figure 17). The data of all ABP 798 lots are within the US-based QR of 0.7-

2.8% and the EU-based QR of 0.7-2.8% (Figure 22 and Figure 26). The EU data are also within the US-based QR (Figure 30).

- **High mannose:** 1.3-2.1% for ABP 798, 1.3-2.8% for US-licensed Rituxan, and 1.2-2.5% for EU-approved MabThera (Table 18 and Figure 18). The data of all ABP 798 lots are within the US-based QR of 0.7-3.0% and the EU-based QR of 0.8-2.8% (Figure 23 and Figure 27). The EU data are also within the US-based QR (Figure 31).
- **Galactosylation:** 55.8-61.8% for ABP 798, 49.5-60.8% for US-licensed Rituxan, and 48.5-61.5% for EU-approved MabThera (Table 19 and Figure 20). The data of all ABP 798 lots are within the US-based QR of 46.9-63.3% and the EU-based QR of 45.4-65.8% (Figure 24 and Figure 28). The EU data are also within the US-based QR (Figure 32).
- **Sialylation:** 2.4-3.8% (mean: 2.99%; SD: 0.39%) for ABP 798, 2.8-5.6% (mean: 4.18%; SD: 0.71%) for US-licensed Rituxan, and 2.7-5.4% (mean: 4.13%; SD: 0.70%) for EU-approved MabThera (Table 20 and Figure 20).

Assessor comment: The ABP 798 lots have slightly lower % sialylation compared to the US and EU products; however, the observed differences in % sialylation are small and lower amounts of sialylation would not be expected to have a negative impact on product efficacy. Furthermore, when the CAA results for % sialylation are analyzed using the QR approach (mean $\pm$ 3 SD), all ABP 798 lots would be within the US-based QR of 2.05-6.31% and the EU-based QR of 2.03-6.23%. Overall, the glycan map by HILIC results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

Extinction coefficient by amino acid analysis (AAA)

Method description and qualification summary: The experimental extinction coefficient of test articles (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is determined by the AAA method and compared to the theoretical extinction coefficient of $1.6 \text{ cm}^{-1}(\text{mg/mL})^{-1}$. The AAA method was qualified for chromatogram precision, retention time precision, and repeatability with up to 4% CV between replicate injections (Table 18, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”).

Assessor comment: The method qualification results support the suitability of the extinction coefficient by AA method for the intended purpose.

CAA lots and test results: One lot each of ABP 798 (a development lot), US-licensed Rituxan, and EU-approved MabThera prepared at 1 mg/mL were analyzed in triplicates each. The experimental extinction coefficients are $1.7 \text{ cm}^{-1}(\text{mg/mL})^{-1}$ for all three products (Table 21).

Assessor comment: The extinction coefficient by AAA results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

pI by capillary isoelectric focusing (cIEF)

Method description and qualification summary: The isoelectric point of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is determined using the cIEF method. The method was previously qualified and verified for accuracy and intermediate precision (Table 19, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”). The verification results show that the method can detect the main, basic and acidic peaks, with up to 0.006 pI unit precision, and that the test pI marker result was accurate to 0.01 pI unit different from the nominal value.

Assessor comment: The method qualification and CAA results support that the pI by cIEF method is appropriate for the intended purpose.

CAA lots and test results: Six lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were assessed side-by-side. Data were generated at the ATO site. The cIEF profiles of ABP 798 are similar to those of the US and EU lots (Figures 33-34), and for all lots evaluated the main peak pI values range between pH 9.4 and pH 9.5 (Table 22).

Assessor comment: *The pI by cIEF results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Identity by ABP 798 ELISA

Method description and qualification summary: The identity of ABP 798, US-licensed Rituxan, and EU-approved MabThera was confirmed using the release test by ABP 798 ELISA method (see method description in Section S.4.2). The method was validated for release testing at the ADL site (see Section S.4.3). The method was also qualified or transferred for use at the ATO AS, ATO QC, AWA, and (b) (4) testing sites. The method qualification results for specificity at the ATO AS and AWA sites show that the positive control appeared indistinguishable in color and intensity and visually distinguishable from the colorless or very light-yellow blank wells (Table 13, response to IR-3, SDN 8). The method transfer summary between ATO Functional Biocharacterization (ATO FB) and ATO QC laboratories states that the transfer is not required, because the procedure, critical reagents, and Laboratory Information Management System (LIMS) assay information of the method are similar to the previous method transfer (Report # 497020, SDN 8). The method transfer report for the transfer from Amgen to (b) (4) show that all of the three ABP 798 DS and two ABP 798 DP samples evaluated by the two analysts passed the specificity and identity test (Table 5, Report # QK-VB-38306e, SDN 8).

Assessor comment: *See Section S.4.3 regarding the adequacy of the method validation result of the ABP 798 identity test method at ADL. The method validation and qualification information and data provided support consistent method performance across all sites with the exception of supportive data provided for performance at ATO QC. Amgen was requested to provide additional information and data to support the method transfer from ATO AS to ATO QC (IR-4). In response to IR-4, Amgen clarified that ATO FB is now part of ATO AS and provided the following information and data.*

Information and data provided in the response to IR-4, SDN 9: The signal-to-noise (S/N) ratios of the reference standard at ATO AS and ATO QC were compared against the assay acceptance criteria of S/N ≥ 10.0 . The results show a S/N ratio of 132-209 for ATO AS (2 assays) and 145-1,146 for ATO QC (19 assays) (Table 3).

Assessor comment: *The reference standard test results support consistent method performance at ATO AS and ATO QC and method transfer between the two sites.*

CAA lots and test results: The total 14 independent ABP 798 lots were evaluated against 3 lots each of US-licensed Rituxan and EU-approved MabThera. Data were generated at the ATO AS, AWA, ATO QC, ADL, and (b) (4) sites. All lots met the acceptance criteria for the identity test (Table 23).

Assessor comment: *The identity by ELISA results provide additional supportive data for a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Higher Order Structure (Document entitled “Analytical Similarity Assessment – Higher Order Structure”)

Secondary structure by Fourier-transform infrared spectroscopy (FTIR)

Method description and qualification summary: The secondary structure such as α -helix, β -sheet and β -turn of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is characterized using the FTIR method. The method was qualified for specificity to ABP 798 over the negative control (formulation buffer) and repeatability as $>95\%$ spectral similarity to the ABP 798 reference standard spectrum (Table 20, document

entitled “Analytical Similarity Assessment – Methods Qualification Summary”). The spectral similarity score was computed from the second derivative spectra in the 1600-1700 cm^{-1} wavelength region using the software function.

Assessor comment: *The method qualification summary with ABP 798 and the FTIR spectra of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support that the FTIR method is suitable for the intended purpose.*

CAA lots and test results: Six lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were side-by-side. The second derivative FTIR spectra of ABP 798 are similar to the spectra of the US and EU lots (Figures 1-5), with $\geq 99.4\%$ spectral similarity (Tables 1-2). The expected antiparallel β -sheet structure is identified using the bands detected around 1,640 cm^{-1} and 1,689 cm^{-1} .

Assessor comment: *The secondary structure by FTIR results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Tertiary structure by near ultraviolet circular dichroism (near UV CD)

Method description and qualification summary: The tertiary structure of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is characterized using the near UV CD method. The method was qualified for specificity to ABP 798 over the negative control (formulation buffer) and repeatability as $>95\%$ spectral similarity to the ABP 798 reference standard spectrum (Table 21, document entitled “Analytical Similarity Assessment – Methods Qualification Summary”). The spectral similarity score was computed from the spectra in the 240-340 wavelength region using the software function.

Assessor comment: *The method qualification summary with ABP 798 and the FTIR spectra of ABP 798, US-licensed Rituxan, and EU-approved MabThera provided as part of the CAA results support that the near UV CD method is suitable for the intended purpose.*

CAA lots and test results: Six lots each of ABP 798, US-licensed Rituxan, and EU-approved MabThera were side-by-side assessed. The near UV CD spectra of ABP 798 are similar to the spectra of the US and EU lots (Figures 7-12), with $\geq 97.3\%$ spectral similarity (Tables 3-4).

Assessor comment: *The same ABP 798, US-licensed Rituxan, and EU-approved MabThera lots were used for CAA of both the FTIR and near UV CD results. The tertiary structure by near UV CD results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Thermal stability by differential scanning calorimetry (DSC)

Method description and qualification summary: The thermal stability profile of the test article (e.g., ABP 798, US-licensed Rituxan, EU-approved MabThera) is measured using the DSC method. The method was qualified at the ATO AS and (b) (4) testing sites, using ABP 798 and an IgG2/4 antibody, respectively (page 7, response to IR-4, SDN 9). The method qualification summaries show no assay interference from formulation buffer at ATO AS for specificity and repeatability standard deviations of 0.02°C for T_{m1} (unfolding of Fab) at ATO AS, 0.2°C for T_{m1} at Elion, 0.07°C for T_{m2} (unfolding of Fc) at ATO AS, and 0.04°C for T_{m2} at (b) (4). (Table 22, document entitled “Analytical Similarity Assessment – Methods Qualification Summary” plus Table 14, response to IR-3, SDN 8).

Assessor comment: *Both the IgG2/4 antibody and ABP 798 are monoclonal antibodies containing Fab and Fc domains, thus the IgG2/4 antibody can be considered sufficiently representative of ABP 798 for the DSC analysis of the two domains. The DSC thermograms provided for ABP 798, US-licensed Rituxan, and EU-approved*

MabThera provided as part of the CAA results support the suitability of the method for these products. The method qualification information and data provided support consistent method performance across all testing sites.

CAA lots and test results: Nine lots each of ABP 798, US-licensed Rituxan, EU-approved MabThera were side-by-side assessed. Data were generated at the ATO AS and (b) (4) sites. The DSC thermograms are similar between the ABP 798, US, and EU lots (Figures 13-15). The observed T_{m1} and T_{m2} values for the ABP 798 lots are within the data range of the US and EU lots (Figures 16-17 and Tables 5-6), and the observed differences are within method capability.

Assessor comment: *The thermal stability by DSC results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Thermal Stability and Degradation Studies (Document entitled “Analytical Similarity Assessment – Thermal Stability and Degradation Studies”; Responses to IR-3 and IR-4)

Assessor note: *Initially, not all of the degradation pathways of ABP 798 identified under elevated temperature, such as methionine and tryptophan oxidation and asparagine deamidation (see Table 42, Section S.3.1), were included in the CAA. Amgen was requested to provide additional information and data to enable an evaluation of all potential degradation pathways (IR-3). In response to IR-3, Amgen indicates that asparagine deamidation is indirectly assessed using % acidic by CEX-HPLC. Considering the intended purpose of this analysis, the minimal changes in deamidation with no significant impact on potency observed for ABP 798 during forced degradation characterization in Section S.3.1), and the totality of the structural and functional comparative data provided, the lack of specific comparative asparagine deamidation data is not considered an issue with respect to the demonstration of highly similar among the three products. Further, Amgen also provided forced degradation by UV light exposure results that includes an assessment of methionine oxidization and tryptophan oxidation.*

Also, due to the impractical presentation of data, an assessment of the degradation rates visually was not possible. Amgen was requested to provide additional analysis to enable a clear and comprehensive evaluation of the degradation rates of ABP 798, US-licensed Rituxan, and EU-approved MabThera (IR-3). In response to IR-3, Amgen provided updated trend charts with trend lines for each lot evaluated in the accelerated, stressed or forced degradation conditions as well as degradation rates (i.e., slope calculated from the time versus percent peak area plot) with p-value for forced degradation results. There was a follow-up IR to clarify the experimental details and results for the forced degradation by UV light exposure study and the stressed stability study (IR-4). The information and data provided in the responses to IR-3 and IR-4 are incorporated into the following sections.

ABP 798, US-licensed Rituxan, and EU-approved MabThera were compared for degradation pathways (e.g., aggregation, fragmentation, charge heterogeneity, CDC potency) under thermal stress at 25°C for 6 months (accelerated), 40°C for 1 month (stressed), and 50°C for 5 days (forced degradation) in addition to UV light exposure at 25 W/m² for up to 24 hours (also see page 48 and Table 7, response to IR-3, SDN 8). For accelerated and stressed storage conditions, all of the 8 stability lots of 100 mg ABP 798 DP were compared to 1 US-licensed Rituxan and 1 EU-approved MabThera lots at the ADL, ATO QC, and AWA testing sites (Table 1). For force degradation by elevated temperature studies, the first 3 clinical ABP 798 DP lots were compared side-by-side with 3 US and 3 EU lots at the AMA site (Table 2). For forced degradation by UV light exposure studies, 1 clinical and 1 PV lot of ABP 798 (lot # 0010324182 and 0010373730) were compared to 1 US lot # 3212064 at the AMA site (page 32, response to IR-3, SDN 8; page 3, response to IR-4, SDN 9). For all studies, the results for % HMW by SE-UHPLC, %HC+LC by rCE-SDS, % pre-peaks by nrCE-SDS, % acidic, % main and % basic by CEX-HPLC, and CDC potency were compared. Methionine oxidation and tryptophan oxidation by reduced peptide map were additionally assessed in the forced degradation by UV light exposure study.

Accelerated (25°C) and stressed (40°C) stability

The accelerated stability data of all lots show similar trends for % HMW increases by SE-UHPLC, % pre-peaks increases by nrCE-SDS, % acidic increases and % main decreases by CEX-UHPLC, and %HC+LC decreases by rCE-SDS with the exception of one ABP 798 lot (Figures 1-6 without trendlines; also see Figures 24-27 and 29 with trend lines, response to IR-3, SDN 8). The ABP 798 lots show minor variability with no practically significant changes in % basic by CEX-UHPLC, while the US and EU lots both show a minor decrease (up to 3% differences over 6 months) in % basic (Figure 28, response to IR-3, SDN 8). The decrease in % basic in the US and EU lots were stated to be attributed to the variability in the conversion of the N-terminal glutamine to pyroglutamate among the three products (all three products have >95% levels of N-terminal pyroglutamate, but US and EU have slightly lower levels). The relative potency values for CDC activity are decreased from 94-126% at 0 month to 52-78% at 6 months for the ABP 798 lots, from 96% to 80% for the US lot, and from 107% to 74% for the EU lot (Figure 7; also see Figure 30 and Table 77, response to IR-3, SDN 8).

The stressed stability data of ABP 798, US-licensed Rituxan and EU-approved MabThera show similar trends as the accelerated stability data (Figures 8-13 without trendlines; also see Figures 31-36 with trend lines, response to IR-3, SDN 8). The relative potency values for CDC activity are decreased from 94-126% at 0 month to 57-92% at 1 month for the ABP 798 lots, from 96% to 83% for the US lot, and from 107% to 93% for the EU lot (Figure 14; also see Figure 37 and Table 78, response to IR-3, SDN 8).

Assessor comment: *The differences in % basic by CEX-UHPLC observed in the accelerated and stressed stability studies are consistent with the results observed in the forced degradation by 50°C studies. The differences between the three products are practically insignificant.*

Because under stressed storage conditions the CDC activity of four of the eight ABP 798 lots evaluated (10261157, 10261159, 10264182, and 10174220, with 31-44% decreases) appear to decrease more rapidly than the US-licensed Rituxan and EU-approved MabThera lots (with 13-14% decreases), Amgen was requested to justify the observed differences in CDC activity between the products (IR-4). Amgen clarified that the ABP 798, US and EU lots were not tested side-by-side and attributed the observed differences to experimental variability such as the stability chamber used and temperature fluctuations, in addition to method variability of the CDC bioassay (page 20, response to IR-4, SDN 9). Amgen also performed additional statistical analysis of the degradation rates for CDC activity described as follows.

Information and data provided in the IR-4 response, SDN 9: The calculated slopes (% relative potency/month) and slope *p*-values for each ABP 798, US-licensed Rituxan, and EU-approved MabThera lots are provided (Table 5). Additionally, pairwise comparisons of the slope differences and adjusted *p*-values between one ABP 798 lot and one US/EU lot were performed using a t-test with Bonferroni adjustment (Table 6). No significant differences (i.e., adjusted *p*-values of ≥ 0.05) are reported for the ABP 798 lots # 0010174220, 0010261157 and 0010261159, whereas a statistically significant difference is noted for one ABP 798 lot 0010324182. The observed difference for the ABP 798 lot 0010324182 was attributed to variability in experimental conditions.

Assessor comment: *Overall, the data and information provided are sufficient to enable an evaluation of the comparative stability data. Considering the limited number of lots evaluated, variability in method performance and experimental design the minor differences appear to be justified. Additionally, more lots of US-licensed Rituxan and EU-approved MabThera were used for the two comparative forced degradation studies (i.e., under elevated temperature, exposed to UV light) against ABP 798 lots in the side-by-side manner, which are discussed below and provide a more robust evaluation of stability and degradation of ABP 798 compared to the other two products. Overall, the accelerated and stressed stability results provided do not preclude a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

Forced degradation by elevated temperature (50°C)

The Day 5 chromatographic or electrophoretic profiles of ABP 798 for SE-UHPLC (Figure 15), rCE-SDS (Figure 17), nrCE-SDS (Figure 19) and CEX-HPLC (Figure 21) are similar to those of US-licensed Rituxan and EU-approved MabThera, with respect to the number, retention time, and shape of the peaks detected. The trend charts and degradation rates of the ABP 798, US and EU lots are summarized below:

- **HMW species by SE-UHPLC:** The levels of the HMW peaks are slightly higher (~1%) in ABP 798 than US-licensed Rituxan and EU-approved MabThera at the initial time point (Figure 16). The degradation rates of the HMW peak were 0.0510-0.0679 %/day for ABP 798, 0.0592-0.1499 %/day for US-license Rituxan, and 0.0842-0.1509 %/day for EU-approved MabThera; the *p*-values are <0.05 for one of the ABP 798 lots (slope: 0.0679) and all of the US and EU lots and >0.05 for the other two ABP 798 lots (Figure 17 and Table 70, response to IR-3, SDN 8).
- **HC + LC by rCE-SDS:** The levels of the HC + LC peaks are slightly lower (~0.5-1%) in ABP 798 than US-licensed Rituxan and EU-approved MabThera at the initial time point and over 5 days (Figure 18). The degradation rates of the sum of HC + LC peaks are from -0.5075 to -0.4251 %/day for ABP 798, from -0.5123 to -0.3705 %/day for US-licensed Rituxan, and from -0.4446 to -0.2892 %/day for EU-approved MabThera; the *p*-values are <0.05 for all ABP 798 and EU lots and two of the US lots (slope: -0.5123 and -0.5107) and >0.05 for the other US lot (Figure 18 and Table 71, response to IR-3, SDN 8).
- **Pre-peaks by nrCE-SDS:** The nr-CE-SDS electropherograms show higher peak intensity for the pre-peaks eluted approximately at 16.0 and 26.0 minutes (Figure 19). The levels of the pre-peaks of the ABP 798 lots are the same as or slightly higher than (up to 1% differences) the US-licensed Rituxan and EU-approved MabThera at the initial time point, and the differences become larger (up to 3% differences) at 3 months and 6 months (Figure 20). The degradation rates of the pre-peaks are 0.3905-0.5961 %/day for ABP 798, 0.2009-0.2129 %/day for US-licensed Rituxan, and 0.1220-0.1922 %/day for EU-approved MabThera; the *p*-values are <0.05 for all lots (Figure 19 and Table 72, response to IR-3, SDN 8).
- **Acidic, main, and basic peaks by CEX-HPLC:** The levels of the acidic peaks of the ABP 798 lots are the same as or slightly higher than (up to 5%) the US and EU lots at the initial time point and after 5 days (Figure 22). The degradation rate for the acidic peaks are 3.0906-3.4932 %/day for ABP 798, 3.3795-3.5046 %/day for US-licensed Rituxan, and 3.2480-3.4466 %/day for US-approved MabThera; the *p*-values are <0.05 for all lots (Figure 20 and Table 73, response to IR-3, SDN 8). The levels of the main peak are similar between the ABP 798, US, and EU lots throughout the study period (Figure 23). The degradation rates for the main peak range between -3.4745 and -3.2582 %/day for ABP 798, between -3.1263 and -2.5984 %/day for US-licensed Rituxan, and between -3.0275 and -2.5350 %/day for EU-approved MabThera; the *p*-values are <0.05 for all lots (Figure 22 and Table 75, response to IR-3, SDN 8). The levels of the basic peaks appear variable with up to 5% differences between the products at the initial time point and 1 month; however, the differences become smaller as time progressed (Figure 24). The degradation rates for the basic peaks range between -0.0708 and +0.1939 %/day for ABP 798, between -0.7811 and -0.3437 %/day for US-licensed Rituxan, and between -0.8122 and -0.4191 %/day for EU-approved MabThera; the *p*-values are <0.05 for all US and EU lots and >0.05 for all ABP 798 lots (Figure 21 and Table 74, response to IR-3, SDN 8).
- **CDC activity:** The relative potency values of the ABP 798 lots are consistently lower (up to 20% difference) than the US and EU lots throughout the study period (Figure 25). The degradation rates for CDC activity range between -3.0177 and -1.7406 %/day for ABP 798, between -2.5605 and -0.8911 %/day for US-licensed Rituxan, and between -1.8048 and -0.6946 %/day for EU-approved MabThera; the *p*-values are <0.05 for all ABP 798 lots and one of the US lots (slope: -2.5605) and >0.06 for all other lots (Figure 23 and Table 76, response to IR-3, SDN 8).

Assessor comment: The degradation rates and profiles of ABP 798, US-licensed Rituxan and EU-approved MabThera are expected to be similar, because the three products have the same DP formulation. The forced degradation results support that the ABP 798 lots have similar degradations rates to the US and EU lots for % HMW by SE-UHPLC, % HC+LC by rCE-SDS, % acidic and % main by CEX-HPLC, and % CDC activity. As discussed for the accelerated and stressed stability results, the observed differences in % basic by CEX-HPLC are

not practically significant. The ABP 798 lots show slightly higher degradation rates for % pre-peaks by nrCE-SDS than the US and EU lots, however, the rates are very slow (<0.5% per day) and the characterization results show that the pre-peaks species present in ABP 798 have negligible impact on potency (see Section S.3.1). Therefore, the forced degradation by elevated temperature results do not preclude a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan and EU-approved MabThera.

Forced degradation by UV light exposure (from response to IR-3, SDN 8)

The post-exposure chromatographic or electrophoretic profiles of ABP 798 for SE-UHPLC (Figure 5), rCE-SDS (Figure 7), nrCE-SDS (Figure 9) and CEX-HPLC (Figures 11-12) appear similar to those of US-licensed Rituxan and EU-approved MabThera, with respect to the number, retention time, and shape of the peaks detected. The stability data provided in tabulated and graphic formats are summarized below:

- **HMW species by SE-UHPLC:** The levels of the HMW, main, and LMW peaks are similar between the ABP 798 and US lots at 0, 8, 16, and 24 hours of UV light exposure (Table 22). The degradation rates for the HMW peaks are 0.61-0.67 %/hour for ABP 798 and 0.74 %/hour for US-licensed Rituxan (Figure 6).
- **HC+LC by rCE-SDS:** The levels of the HC+LC, LMW, LC, MMW, NGHC, HC, post-HC, and HMW species are similar between ABP 798 and US-licensed Rituxan at 0, 8, 16, and 24 hours of UV light exposure (Table 23). The degradation rates for the sum of the HC and LC peaks range between -0.289 and -0.300 %/day for ABP 798 and is -0.308 %/day for US-licensed Rituxan (Figure 8).
- **Pre-peaks by nrCE-SDS:** The levels of the pre-peaks and main peak are similar between ABP 798 and US-licensed Rituxan at 0, 8, 16, and 24 hours of UV light exposure (Table 24). The degradation rates for the pre-peaks are 0.61-0.67 %/hour for ABP 798 and 0.74 %/hour for US-licensed Rituxan (Figure 10).
- **Acidic, main, and basic peaks by CEX-HPLC:** The levels of the acidic, main, and basic peaks are similar between ABP 798 and US-licensed Rituxan at 0, 8, and 16 hours of UV light exposure (Table 25; Figures 13-15). For the acidic peaks, the degradation rates are 2.00-2.10 %/hour for ABP 798 and 2.06 %/hour for US-licensed Rituxan. For the main peak, the degradation rates range between -2.39 to -2.17 %/hour for ABP 798 and is -2.27 %/hour for US-licensed Rituxan. For the basic peaks, the degradation rates are 0.16-0.28 %/hour for ABP 798 and 0.21 %/hour for US-licensed Rituxan.
- **Methionine oxidation and tryptophan oxidation by reduced peptide map:** The samples were treated at 50°C for 0, 8, and 16 hours and analyzed for methionine oxidation at HC M34, HC M432 and HC M256 and for tryptophan oxidation at HC W106 and LC W90 (Table 26, response to IR-3, SND 8). The extent of HC M34 oxidation is increased from 2% to 2-3% for ABP 798 and from 1% to 2% for US-licensed Rituxan. The extent of HC W106 oxidation is increased from 5-8% to 41-44% for ABP 798 and from 2% to 38% for US-licensed Rituxan. The extent of HC M432 oxidation is increased from 3% to 21-23% for ABP 798 and from 3% to 26% for US-licensed Rituxan. The extent of HC M256 oxidation is increased from 5-6% to 21-23% for ABP 798 and from 4% to 25% for US-licensed Rituxan. The extent of LC W90 oxidation is not detected before exposure and increased to 4% for all ABP 798 and US lots after 16 hours of UV light exposure.
- **CDC activity:** The relative potency values were assessed for ABP 798 and US-licensed Rituxan at 0, 8, and 16 hours of UV light exposure (Table 27). The degradation rates for CDC activity range between -3.38 and -2.94 %/hour for ABP 798 and is -2.81 %/hour for US-licensed Rituxan (Figure 16).

Assessor comment: *No EU-approved MabThera lot was used in this study. However, considering that the forced degradation by elevated temperature study has captured most of the degradation pathways for all three products and that the additional methionine oxidation and tryptophan oxidation results from the UV light exposure study show no significant differences between ABP 798 and US-licensed Rituxan, the information provided is sufficient to enable an evaluation of the possible degradation pathways of ABP 798, US-licensed Rituxan, and EU-approved MabThera.*

A discrepancy between the forced degradation by UV light exposure results from the CAA and characterization studies of ABP 798 was noted, in which larger decreases in CDC activity were observed in the CAA study compared to the characterization data (Section S.3.1). Amgen was asked to clarify the observed discrepancy (IR-4). In response to the IR, Amgen stated that the experimental conditions differed in protein concentration (~10 mg/mL for CAA and ~50 mg/mL for characterization) and vial dimensions (inner diameter of 8 mm for CAA and 28 mm for characterization) (Table 1, response to IR-4, SDN 9). Thus, the CAA results were generated using a higher overall UV exposure per mg protein. This justification is reasonable.

The ABP 798 lots show similar degradation rates to the US-licensed Rituxan lot, with respect to % HMW by SE-UHPLC, % HC+LC by rCE-SDS, % pre-peaks by nrCE-SDS, % acidic, % main and % basic by CEX-UHPLC, methionine oxidation, tryptophan oxidation, and relative potency for CDC activity. Therefore, the forced degradation by UV light exposure results support a demonstration of highly similar and establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera.

Overall assessor conclusion on comparative analytical assessment between ABP 798, US-licensed Rituxan and EU-approved MabThera: The information and data provided show that the ABP 798 have slightly different impurity profiles from the US and EU rituximab products, e.g., types and relative abundance of the HMW species detected by SE-UHPLC and other analytical methods, forces degradation rates of % pre-peaks by nrCE-SDS. However, the CAA results for biological activity, including CDC activity, ADCC activity, Fc receptor binding, C1q binding and apoptosis, show that the minor differences observed in impurities are not extensive enough to impact biological activity, which is demonstrated as similar among the three products. Furthermore, the CAA results for primary structure and secondary structure further support that ABP 798 has highly similar structure to the US and EU products. The strength of US-licensed Rituxan is labeled in mass per unit volume (mg/mL). US-licensed Rituxan is filled into vials with a volume of 10 mL and 50 mL. Amgen is seeking approval for the same strength as US-licensed Rituxan. Comparative protein concentration (mg/mL), assessed as part of the CAA, deliverable volume (assessed as part of the CAA) and fill weight data assessed as part of manufacturing process controls were used to inform the assessment of whether the proposed presentation of ABP 798 has the same strength as the presentation of US-licensed Rituxan. Based on the similarity and manufacturing data, the 100 mg/10 mL and 500 mg/50 mL of ABP 798 has the same total content of drug product in units of mass in a container and the same concentration of drug product in unit of mass per unit volume as the presentations of US-licensed Rituxan. This presentation meets the statutory “same strength” requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act. Based on the totality of evidence provided, we agree that ABP 798 is highly similar to US-licensed Rituxan, and the data and information further support establishment of the three-way analytical bridge between ABP 798, US-licensed Rituxan and EU-approved MabThera.

3.2.R.1 Executed Batch Records

The batch records for the ABP 798 DS lot # 0010356678 manufactured at ARI as well as ABP 798 100 mg DP lot # 0010373730 and ABP 798 500 mg DP lot # 0010373733 manufactured at (b) (4) are provided. The certificate of analysis documents for the four DS PV lots and the six DP PV lots are also included.

Assessor comment: The three lots were used for process validation of the ABP 798 DS or DP manufacturing processes. The information and data in the batch records are consistent with the BLA.

3.2.R.2 Method Validation Package

The method validation reports and analytical procedure protocols are provided for the analytical methods used for in-process, release, and/or stability testing of ABP 798.

Assessor comment: The adequacy of the information and data provided method documents are described and discussed in the related sections, e.g., S.4.2, S.4.3, P.5.2, P.5.3.

3.2.R.3 Comparability Protocols

No comparability protocols are provided.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

One anti-drug antibody (ADA) and one neutralizing ADA (NAb) assay was developed to detect binding ADA and NAb developed against ABP 798, US-licensed Rituxan, or EU-approved MabThera in patient samples, respectively. The ADA and NAb detection methods were used to evaluate samples from the RA PK similarity/comparative clinical study (Study # 20130108) and the NHL comparative clinical study (Study # 2030109). The test samples (i.e., human serum aliquots) for the ADA and NAb assays were stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ prior to testing. The ADA test method is an electrochemiluminescence (ECL)-based bridging assay. For screening, ADAs are captured using a biotinylated ABP 798 and a ruthenylated ABP 798 in the presence of ofatumumab (to prevent potential assay interference from CD20); the captured complex with the biotin tag is indirectly immobilized onto a streptavidin-coated microtiter plate, in which the ruthenium-containing complex reacts with tripropylamine (TPA) and results in an increase in ECL signals measured using a MSD plate reader.

For confirmation, the same ADA assay reagents plus soluble ABP 798 are used. The ADA complex in the sample is dissociated prior to analysis by diluting the test sample to 5% human serum containing 300 mM acetic acid. The NAb testing method is an ADCC reporter bioassay, in which binding between ABP 798, CD20-expressing WIL2S cells, and CD16-expressing engineered NK92 cells results in ADCC and subsequent NFAT-driven luciferase reporter gene expression in the engineered cells; binding of ABP 798 by NAb results in a decrease in luciferase signals measured by an Envision plate reader.

Both ADA and NAb test methods are performed using a 2-tier approach consisting of screening and confirmatory assays. The presence of NAb in the test sample is confirmed by immunodepleting the NAb from the sample using a mixture of Protein G and Protein L immobilized on agarose beads. The samples test positive for NAb are further analyzed in the titration assay, and the highest dilution yielding a positive result is reported.

ADA detection assay (Report # ICDIM 239 Version 1.00)

The ADA detection assay was validated at PPD, Richmond, VA, using a clinical ABP 798 DP lot # 0010261157. The low and high positive controls used are in-house mouse anti-ABP 798 mAb in pooled healthy human serum at 10.0 ng/mL (LPC) and 500 ng/mL (HPC). The negative control (NC) is a pooled drug-naïve sample from 12 individuals with no detectable ADA.

Cut point determinations:

The screening assay cut point was determined based on the ADA test results of 30 individual human serum samples each from RA or NHL patients with no detectable ADA (Appendix D). The confirmatory assay point was determined based on the ADA results of the 30 spiked samples per disease state population; the samples were spiked with 25 µg/mL excess drug prior to analysis (Appendix E). Each individual sample was evaluated in four independent assays by two different analysts (i.e., 120 assay values). The screening and confirmatory assay results were provided as S/N and % depletion, respectively (Table 1). The statistical outliers were identified using Tukey's method and excluded from further analysis. The screening cut point (SCP) and confirmatory cut point (CCP) were determined using a non-parametric approach with 5% false positive discovery rate (FPDR) and a parametric approach with 1% FPDR, respectively.

- **SCP:** The analysis of the run means and variances suggests a fixed cut point for SCP. The SCP values are S/N ratios of 1.38 for RA patient samples (115 assay values) and 0.88 for NHL patient samples (103 assay values).
- **CCP:** The RA and NHL data show a normally distribution. The CCP values are 18.7% depletion for RA patient samples (113 assay values) and 2.40% depletion for NHL patient samples (103 assay values).

Assessor comment: The SCP and CCP are appropriately derived.

Precision:

The assay was evaluated using the NC, LPC, and HPC. Each control was tested in six independent assays for intra-assay precision (Table 4), and the control data from 26 validation runs were used for inter-assay precision (Table 5). The screening assay has an intra-assay precision of 4% for NC and 2% for LPC and HPC; as well as well as an inter-assay precision of 13% for NC, 9% for LPC, 10% for the second LPC at 25.0 ng/mL, and 14% for HPC. The confirmatory assay has an intra-assay precision of 2% for NC, 3% for LPC and 5% for HPC; as well as an inter-assay precision of 12% for NC, 4% for LPC, 6% for the second LPC, and 12% for HPC.

Assessor comment: *The results provided support that the ADA assay is sufficiently precise.*

Sensitivity and Hook effect:

The assay was evaluated in four independent assays by two analysts, using a 1:2 dilution series of the positive control from 80.0 ng/mL to 0.625 ng/mL (Tables 6A and 6B). The assay sensitivity values are 5.99 ng/mL for the screening assay and 4.67 ng/mL for the confirmatory assay.

A separate dilution series of the positive control at 0.500-1,024 µg/mL were used to evaluate the potential Hook effect (Table 7). No apparent Hook effect is observed for up to 1,024 µg/mL.

Assessor comment: *The assay sensitivity level is below the LPC concentration of 10 ng/mL. The results provided support that the ADA assay is sufficiently sensitive.*

Specificity, selectivity and cross-reactivity:

For evaluation of potential matrix interference, the NC, LPC and HPC were spiked with 5.00 or 10.0 mg/mL hemoglobin, 1:10 or 1:20 diluted intralipid, 0.200 or 0.500 mg/mL of conjugated or unconjugated bilirubin and tested for ADAs (Table 10). No interference on ADA detection from hemolysis, lipemia, or bilirubin is observed.

For determination of the lower limit of reliable detection (LLRD) of the ADA detection assay, 15 each of individuals in RA or NHL disease-state and initial negative screening results were selected. The human serum samples from these individuals were spiked with LPC. All spiked samples tested positive (Table 11).

For evaluation of potential target interference, the NC and LPC fortified with 100.0, 50.0, 10.0, and 0.0 µg/mL CD20 were incubated with 150 ng/mL to 300 µg/mL of ABP 798 in pooled healthy human serum, or without ABP 798 (Table 15). All NC samples were screened negative. No assay interference from up to 100 µg/mL CD20 to the LPC samples is observed.

Further, 15 patient samples each of the RA and NHL disease state populations treated with ABP 798, US-licensed Rituxan, or EU-approved MabThera were prepared at 10.0 ng/mL and evaluated using the ADA assay; samples from blank donors were also included as a negative control (Tables 12, 13A, and 13B). All samples treated with ABP 798, US-licensed Rituxan, or EU-approved MabThera tested ADA-positive.

Assessor comment: *The results indicate that the assay specifically detects the ADAs against ABP 798, US-licensed Rituxan, and EU-approved MabThera, with neglectable interference from the matrix and target. The LLRD results indicate that the assay can reliably detect ADA concentrations at 10.0 ng/mL (LPC) and above.*

Drug tolerance:

The NC, LPC (10 ng/mL), HPC (500 ng/mL), and 1,000 ng/mL ADAs were spiked with 10, 50, 100, and 200 µg/mL of ABP 798, US-licensed Rituxan, or EU-approved MabThera (Tables 14A, 14B, and 14C). The assay is shown capable of detecting 10 ng/mL of ADAs in the presence of 50.0 µg/mL ABP 798 and 500 ng/mL and 1,000 ng/mL of ADAs in the presence of up to 200 µg/mL ABP 798. The assay is also tolerant to 50.0 µg/mL of US-licensed Rituxan or 100 µg/mL of EU-approved MabThera in the presence of 10 ng/mL ADAs and up to 200

µg/mL of US-licensed Rituxan or EU-approved MabThera in the presence of 500 ng/mL and 1,000 ng/mL of either products.

Assessor comment: *As the maximum study drug serum concentration for the NHL study (i.e., 0.54-59.64 µg/mL for ABP 798, 0.81-66.20 µg/mL for US-licensed Rituxan, 0.85-72.68 µg/mL for EU-approved MabThera) and the RA study (i.e., 16.69-221.30 µg/mL for ABP 798, 18.50-229.90 µg/mL for US-licensed Rituxan) was very close or much lower than 200 µg/mL, the ADA assay drug tolerance would allow for the detection of at least 500 ng/mL and up to 1,000 ng/mL of ADAs at serum drug levels relevant to clinical patient sampling time points. While recent data suggests that concentrations of ADAs as low as 100 ng/mL may be associated with clinical events, the determined sensitivity of this ADA binding assay is reasonable considering FDAs traditional recommendation of an assay sensitivity of at least 250-500 ng/mL. Further, because drug tolerance was evaluated only in the presence of 10 ng/mL and 500 ng/mL, it is possible that the assay has a lower level of sensitivity between the two studied concentrations in the presence of clinically relevant on-board drug concentrations. This is acceptable.*

In-use stability:

The freeze-thaw stability was evaluated using NC, LPC, and HPC, which underwent five freeze-thaw cycles versus freshly prepared (Tables 8A, 8B, and 8C). The controls are shown stable (i.e., <5% CV) for up to three freeze-thaw cycles between -80°C±10°C and room temperature.

The thaw matrix stability was evaluated using thawed or freshly prepared LPC and HPC (Table 9). The thaw matrices are shown stable (i.e., up to 11% differences in S/N mean between thawed versus freshly prepared) for 168 hours at 2-8°C and 24 hours at room temperature; all NC tested negative and all LPC/HPC tested positive.

Assessor comment: *The results indicate that clinical patient samples are expected stable over temporary storage at room temperature or 2-8°C with and without freeze-thaw.*

Assessor Overall Conclusion on ADA Method Validation: *The validation data and information provided for the ADA detection method support the use of this method for interpretation of the immunogenicity results derived from patient samples collected during the RA and NHL clinical studies.*

NAb detection assay (Report # VSDCBA 67 and Addendum 1)

Assessor note: *The initial method validation study yielded unacceptable results for bilirubin interference. The addendum is to provide additional re-validation run data for bilirubin interference as well as validation of the method for potential target interference.*

The NAb detection assay was validated at PPD, Richmond, VA, using the same ABP 798 DP lot for the ADA detection assay. The PC (i.e., anti-ABP 798 antibody) concentration used during method validation was changed from 600 ng/mL for evaluation of SCP, sensitivity and LLRD to 200 ng/mL based on the LLRD result. The drug qualification/cross validation studies using ABP 798, US-licensed Rituxan or EU-approved MabThera show that several samples spiked with 200 ng/mL ADAs had negative screening/confirmatory results in the presence of up to 400 ng/mL of study drug; and that two spiked samples tested positive with 200 ng/mL ADAs but negative with 400 ng/mL ADAs (Tables 14-16). Four additional individual samples were evaluated, and all the unspiked and spiked samples tested negative and positive, respectively (Table 17). The PC concentration was adjusted to 400 ng/mL for further method validation and immunogenicity testing. A NC and a drug control (DC) are also used. The screening assay values above the SCP are defined as “negative” for the presence of NAb, and the values at or below the SCP are defined to be “confirmation required”. The confirmatory assay values above the CCP are defined as “positive” for the presence of NAb, and the values at or below the CCP are defined as “negative”.

Assessor comment: *The final PC concentration of 400 ng/mL is also determined based on the drug tolerance results (see the drug tolerance section in the following).*

Cut point determinations:

The SCP and CCP were determined based on the NAb test results of 25 individual human serum samples each from RA or NHL patients (see Appendix C). For SCP and CCP determinations, each individual was evaluated in at least three independent assays by at least two different analysts on at least two days. The assay values were log-transformed and evaluated using Shapiro-Wilk normality test and skewness coefficient. The statistical outliers were removed using a parametric method with Tukey's procedure. The cut points were determined using a parametric method, with 5% FPER for SCP and 1% FPER for CCP.

- **Screening cut point:** The parametric estimate for the fixed SCP is 0.722, based on the 95 screening assay results from 33 donors (Tables 2-3).
- **Confirmatory cut point:** The parametric estimate for the fixed CCP is 1.22, based on the 104 confirmatory assay results from 35 donors (Table 4).

Assessor comment: *The SCP and CCP are appropriately derived.*

Precision:

For intra-assay precision, the PC at 200 ng/mL was evaluated in six assays in six replicates. For inter-assay precision, the results for the PC at 200 ng/mL (28 runs), 400 ng/mL (14 runs), and 600 ng/mL (24 runs) from the acceptable runs were evaluated. The assay has an intra-assay precision of 1.30% for the 200 ng/mL PC and 10.6% for the 400 ng/mL PC (Table 18), as well as an inter-assay precision of 18.5% for the DC/PC ratio and 18.9% for the CPC/DC ratio with 400 ng/mL PC (Table 21). The assay also has an inter-assay precision of 14.2% for the DC/PC ratio and 12.8% for the CPC/DC ratio with 600 ng/mL PC (Table 19) and 10.6% for the DC/PC ratio and 6.79% for the CPC/DC ratio with 200 ng/mL PC (Table 20).

Assessor comment: *The results support that the NAb assay using the PC at 400 ng/mL is sufficiently precise considering that this assay is cell-based.*

Sensitivity and LLRD:

The NC was spiked with ADAs in 11 concentrations at 0.00102-50.0 µg/mL in healthy human serum and tested as duplicates in three independent assays by two analysts on at least two days; the assay sensitivity determined from the analysis is 48.6 ng/mL with a mean screening assay value of 0.706 (Table 5). Samples from six individual RA/NHL disease state individuals were spiked with 48.6-500 ng/mL ADAs and analyzed; the LLRD determined from the analysis is 400 ng/mL (Tables 6-8).

Assessor comment: *The NAb detection assay is sufficiently sensitive considering this is a neutralization assay. While sensitivities of ~100 ng/mL may have clinical relevance, a sensitivity this low is not always reasonable for neutralization assays. Traditionally, FDA expects an assay sensitivity of 250-500 ng/mL. Based on the totality of the assay validation data (e.g., drug qualification/cross validation data), the LLRD was adjusted from 200 ng/mL to 400 ng/mL. This is reasonable. See additional discussion below considering the determined assay sensitivity with respect to clinically relevant on-board drug concentrations.*

Specificity, selectivity and serum interference:

Thirty-seven cut point determinations samples were tested unspiked or spiked with 200 ng/mL of PC. The unspiked samples of 36 of 37 individuals tested negative, and the PC-spiked samples of 34 of 37 individuals tested positive (Table 9).

Six human serum samples from healthy individuals were spiked with 1%, 5% or 10% hemolyzed matrix and then tested unspiked or spiked with 400 ng/mL PC. All unspiked and spiked samples tested negative and positive, respectively (Tables 25-27).

Six human serum samples with >300 mg/dL triglycerides were also tested unspiked or spiked with 200 ng/mL PC. Five of the six unspiked lipemic samples tested negative, and all spiked lipemic samples tested positive (Table 28).

Six human serum samples from commercial individuals were tested for NAb unspiked or spiked with ≥ 20.0 mg/dL bilirubin, and two of the unspiked samples were determined positive for NAb (Table 29). The method was revalidated using the serum samples prepared from three individuals each with NHL or RA spiked with 20.0 mg/dL bilirubin. Another replicate set is further spiked with 400 ng/mL PC. The screening and confirmatory assay results of the unspiked and PC-spiked samples are reported as negative and positive, respectively (Table 3, Report # VSDCBA 67 Addendum 1).

Target interference on NAb detection was evaluated by spiking the NC pool at ten different sCD20 concentrations ranging from 0.0586 $\mu\text{g/mL}$ to 30.0 $\mu\text{g/mL}$. The highest sCD20 concentration that yielded a negative screening assay result is 7.50 ng/mL (Table 2, Report # VSDCBA 67 Addendum 1).

Assessor comment: *The results support specificity of the NAb assay. No assay interference is observed under the hemolysis, lipemia, and target concentration conditions evaluated.*

Drug tolerance:

The test samples are prepared via 1:1 dilution to a final concentration of 0.781-400 ng/mL ABP 798, with a spiked PC amount of 200 ng/mL or 400 ng/mL. The assay is shown capable of detecting 400 ng/mL of PC in the presence of up to 200 ng/mL ABP 798; and 800 ng/mL of PC in the presence of up to 400 ng/mL ABP 798 (Tables 10-11). Samples spiked with 200 ng/mL PC in the presence of 0.781-400 ng/mL ABP 798 were negative.

Assessor comment: *The sensitivity of the assay was overall determined to be 400 ng/mL (0.4 $\mu\text{g/mL}$) PC. In the presence of 0.4 $\mu\text{g/mL}$ of ABP 798 at a PC concentration of 0.4 $\mu\text{g/mL}$, neutralizing activity was detectable. The mean range of the serum concentrations of study drugs (ABP 798, US-licensed Rituxan, EU-approved MabThera) in clinical study 20130108 was 0.54 to 72.68 $\mu\text{g/mL}$; because the low incidence of ADAs in study 20130109, impact of ADAs on efficacy were not assessed by the clinical pharmacology team. The NAb assay validation study did not provide sufficient information to demonstrate that neutralization activity is detectable in the presence of the range of clinically relevant on-board drug levels (i.e., above 0.4 $\mu\text{g/mL}$). However, per the clinical pharmacology reviewer information, the clinical immunogenicity data show that NAb were detected at baseline, weeks 24, 30, and 48 across all study drugs even in the presence of on-board drug concentrations higher than 0.4 $\mu\text{g/mL}$. The clinical pharmacology reviewer also determined that the magnitude of impact of ADA and PK was comparable between ABP 798 and the comparator products, and that there was no impact of ADA on efficacy. Further, considering the historically low impact and incidence of ADA/NAb with respect to Rituximab, the low drug tolerance of the NAb assay is not likely to impact an immunogenicity safety assessment. Nevertheless, this was communicated to the clinical pharmacology reviewer to inform the overall evaluation of the impact of ADAs on efficacy. The Clinical Pharmacology Review team agreed with the risk assessment, and that given the low ADA incidence in general, and the ability of the Nab assay to detect Nabs in clinical samples even at drug concentrations above the tolerance level demonstrated in the method validation, the overall method validation results do not impact the assessment of the Nab assay when evaluating the clinical samples.*

Antibody titer:

Sample titer reproducibility was evaluated using pooled human serum spiked with 1.00, 5.00 and 25.00 mg/mL of PC, with a dilution of 1:500 (i.e., Dil 500), 1: 2,500 and 1:12,500; the samples correspond to 5-folds, 25-folds, and 125-folds of the PC at 200 ng/mL. The highest titers reported are Dil 500 at 1.00 $\mu\text{g/mL}$, Dil 2,500 at 5.00 $\mu\text{g/mL}$, Dil 12,500 at 25.0 $\mu\text{g/mL}$, and Dil 12,500 at 50.0 $\mu\text{g/mL}$ (Tables 12-13).

Assessor comment: *The antibody titers are appropriately derived.*

In-use stability:

The PC at 400 ng/mL underwent six freeze-thaw cycles, in which the sample was frozen at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ for at least 24 hours for the first cycle and for at least 12 hours for the other five cycles before thawing at room temperature. The samples were then analyzed in six replicates. The PC is shown stable (i.e., screening assay values below SCP) for 6 freeze-thaw cycles (Table 22). The thaw matrix is also shown stable for up to 7 days at $2-8^{\circ}\text{C}$ and for up to 24 hours at room temperature (Tables 23-24).

Assessor comment: *The results indicate that clinical patient samples are expected stable over temporary storage at room temperature or $2-8^{\circ}\text{C}$ with and without freeze-thaw.*

Assessor Overall Conclusion on NAb Method Validation: *The method validation data combined with clinical immunogenicity test results support that the NAb detection method is generally acceptable with respect to the detection of NAb in the presence of low levels of ABP 798 in clinical samples.*



Amy
Hsu

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U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
Division of Biotechnology Manufacturing

PRODUCT QUALITY MICROBIOLOGY REVIEW/FACILITY ASSESSMENT
Memorandum of Review to the File (Drug Product)

Primary Reviewer: Amy Devlin, Ph.D.

Secondary Microbiology Reviewer: Maxwell Van Tassell, Ph.D.

Secondary Facilities Reviewer: Thuy Thanh Nguyen, DHSc.

BLA: 761140/0

Applicant: Amgen, Inc.

US License Number: 1080

Product: RIABNI (ABP 798; rituximab-arrx)

Indication: Treatment of adult patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, or pemphigus vulgaris

Dosage Form: Solution for IV infusion, 100 mg/10 mL and 500 mg/50 mL

Facility: (b) (4)

FDA Receipt Date: December 19, 2019

Action Date: December 19, 2020

Conclusion and Approvability Recommendation

The drug product portion of BLA STN 761140/0, as amended, was reviewed from a sterility assurance perspective and is recommended for approval. The drug product facility assessment recommendation is approval. Refer to the memo from Dr. Zhong Li for an assessment of the drug substance section of the BLA.

REVIEW SUMMARY

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	12/19/2019	Original BLA
0007	04/24/2020	Amendment (Response to IR)
0010	06/17/2020	Amendment (Response to IR)
0015	08/11/2020	Amendment (Response to IR)

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) proposed for ABP 798 DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their cGMP compliance status and recent relevant inspectional coverage. The submission is recommended for approval from a facility standpoint.

1.14 LABELING

2 Dosage and Administration



Reviewer Comment: See microbial challenge studies in section 3.2.P.2.6. The proposed storage times are based on microbial data.

MODULE 3.2 – RIABNI (ABP 798; RITUXIMAB-ARRX FOR INJECTION, 100 MG/VIAL OR 500 MG/VIAL)

P.1 Composition of the Drug Product

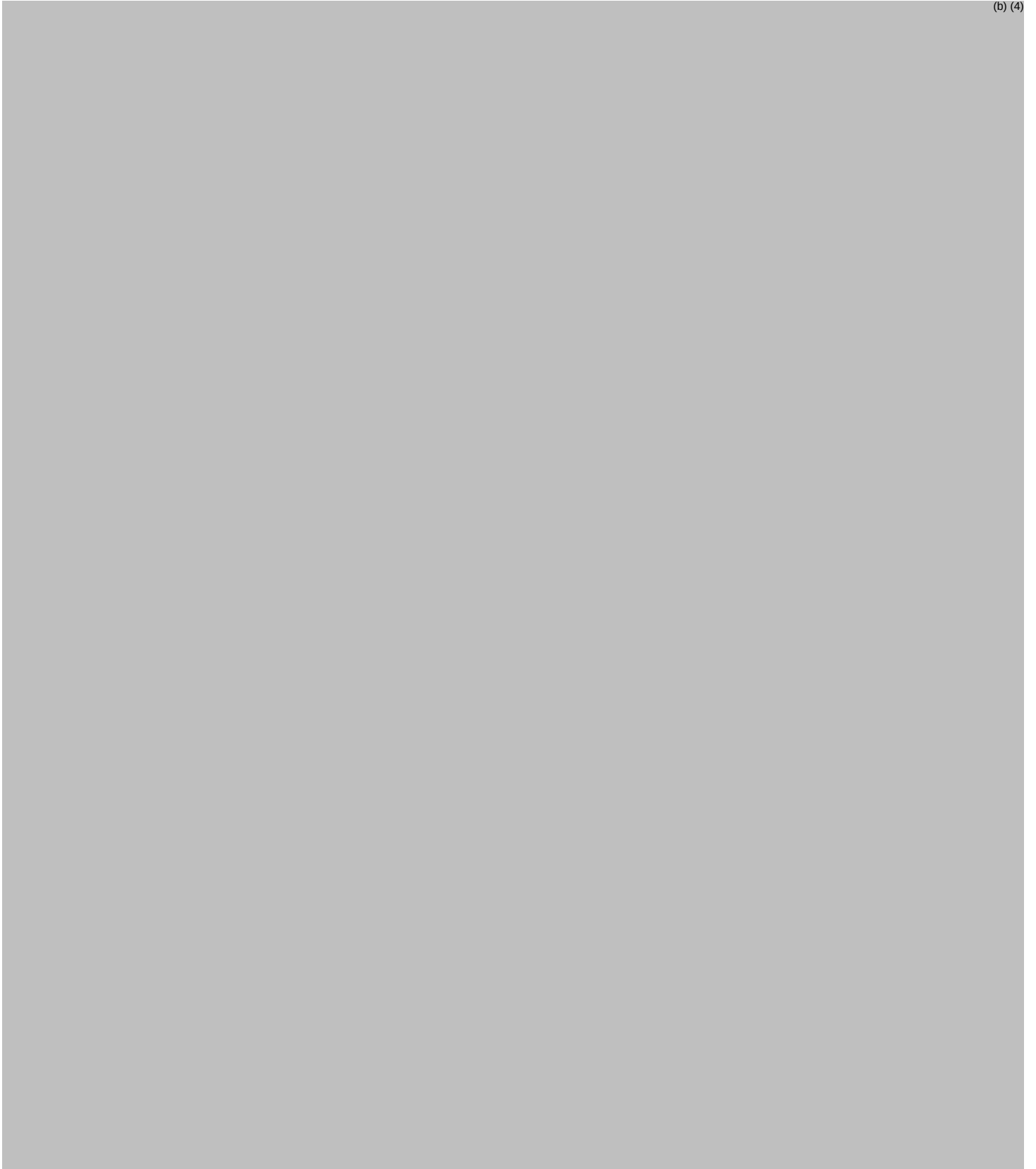
ABP 798 DP is a sterile, preservative-free, solution for intravenous infusion provided in single-use, 10 cc (100 mg dose) or 50 cc (500 mg dose) (b) (4) glass vial. The composition of ABP 798 DP was provided in Table 1 in Module P.1 (table not shown herein). The 10 cc vial contains 100 mg ABP 798 DS, 90.0 mg sodium chloride, 73.5 mg sodium citrate dihydrate, 7.0 mg polysorbate 80, hydrochloric acid to adjust pH to 6.5 as needed, and WFI qs to target volume. The 50 cc vial contains 500 mg ABP 798 DS, 450.0 mg sodium chloride, 367.5 mg sodium citrate dihydrate, 35.0 mg polysorbate 80, hydrochloric acid to adjust pH to 6.5 as needed, and WFI qs to target volume.

Reviewer Comment: The composition of ABP 798 DP was adequately described.

—SATISFACTORY—

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)



27 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

—SATISFACTORY—

(b) (4)

P. 8 Stability

The proposed shelf life for ABP 798 drug product is 36 months at 2-8°C. At least one commercial batch of DP will be added to the post-approval stability program each year. Sterility testing will be performed at release (time 0). CCIT will be performed annually thereafter for the duration of the shelf-life at recommended storage.

CCIT results pass acceptance criteria for all time points for lots stored at 2-8°C as shown in 3.2.P.8.3 *Stability Data*.

—SATISFACTORY—

CONCLUSIONS

- 1. The drug product section of this BLA, as amended, was reviewed from a sterility assurance perspective and is recommended for approval.**
- 2. Product quality aspects not related to microbial control should be reviewed by OBP.**
- 3. Refer to Panorama for the cGMP compliance status of the relevant facilities.**

INFORMATION REQUESTS

IR Submitted 04/09/2020

Response received 04/24/2020 in Sequence 0007.

3.2.P.5.1 and 3.2.P.5.6

6. With regard to the proposed ABP 798 release specifications, provide the endotoxin specifications for the drug substance and drug product in EU/mL as this is a liquid product and the read out of the assay is in EU/mL. Additional calculations for the conversion to EU/mg may introduce variability. Update Section 3.2.S.4.1 and all other relevant sections in the BLA accordingly.

IR Submitted 01/30/2020

Response received 06/17/2020 in Sequence 0010.

3.2.P.3.5

1. Data were provided for the media fill simulations conducted with the (b) (4) container closure systems (CCS); however, these CCS are not representative of the commercial drug product. Provide data for at least one media fill conducted with the 10 cc and 50 cc vial CCS used for the commercial drug product.

IR Submitted 07/29/2020

Response received 08/11/2020 in Sequence 0015.

3.2.P.3.3 and 3.2.P.3.5

25. Provide a summary description for the filtration study referred to in Tables 20 and 21 of P.3.5 Process Validation, including the type of pump and tubing used, the data to establish that the sterile filtration cannot exceed validated pressure using the maximum pump speed setting. Update Section P.3.3 to include the diameter of the tubing to be used with the pump for the sterile filtration step.

26. Provide descriptions (manufacturer, model, equipment ID #, etc.) of the critical equipment (b) (4) proposed for routine production of the drug product and confirm that the validation data provided in the submission for (b) (4) were performed using the proposed equipment.



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Devlin

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Maxwell
Van Tassell

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**PRODUCT QUALITY MICROBIOLOGY/FACILITY
ASSESSMENT****Memorandum of Review to the File (Drug Substance)**

Application ID	BLA 761140
Drug Product Name	Rituximab-arrx (ABP 798)
Strengths	100 mg/10 mL or 500 mg/50 mL
Dosage Form	Liquid solution for intravenous infusion
Administration Route	Intravenous infusion
Indication	Non-Hodgkin's Lymphoma
Applicant Name	Amgen Inc.
US License Number	1080
Application Type	351 (k)
Primary Reviewer(s)	Zhong Li, Ph.D., Reviewer, CDER/OPQ/OPMA/DBM/Branch 1
Secondary Reviewer(s)	Maxwell Van Tassell, Ph.D., Microbiologist, OPMA/DBM/Branch 1 (microbiology) Thuy Nguyen, DHSc., Branch Chief, OPQ/OPMA/DBM Branch 1 (facility)
Goal Date	December 19, 2020

Recommendation for Approvability:

- The drug substance portion of this BLA was reviewed from a microbial control and product quality microbiology standpoint and is recommended for Approval.
- Drug Substance Facility Assessment Recommendation: Approval

Summary Basis of Recommendation:

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4)

Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Immunex Rhode Island Corporation (FEI 3003359885), proposed for Rituximab-arrx (ABP 798) DS manufacture. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Endotoxin	Safety, Purity	Raw materials, manufacturing process	(b) (4)	—
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process		—

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original Submission/0001	12/19/2019
Response to IR/0007	4/24/2020

Module 3.2.S Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations:	No

S.1 General Information

Rituximab-arrx (ABP 798) is a genetically engineered chimeric mouse/human IgG1 monoclonal antibody that specifically binds to the CD20 antigen expressed on B cells and promotes B-cell depletion through multiple mechanisms. The approximate molecular weight is 147 kDa. ABP 798 DS is produced from a CHO-derived production cell line, (b) (4)

Reviewer's Comment: For Information

S.2 Manufacture**S.2.1 Manufacturer(s)**

Facility Name and Address	FEI	Responsibilities and profile code(s)	Status
Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI) 40 Technology Way, West Greenwich, Rhode Island, United States of America, 2817	3003359885	Drug substance manufacture; in-process, lot release, and stability testing; Working cell bank storage; Unprocessed bulk testing: mycoplasma CBI	Approve - Based on PAI/PLI
Amgen Inc. (Referred to as Amgen Thousand Oaks or ATO) One Amgen Center Drive, Thousand Oaks, California, United States of America, 91320	2026154	Drug substance in-process testing: glycan map*; Master cell bank and working cell bank storage; Working cell bank manufacture; Drug product lot release and stability testing CBI	Approve - Based on Previous History
(b) (4)		Mycoplasma testing, Adventitious viral testing (unprocessed bulk) LBI	Approve - Based on Previous History

Amgen Technology Ireland UC (Referred to as Amgen Dun Laoghaire or ADL) Pottery Road , Dun Laoghaire, Ireland	3002808497	Drug substance in-process, lot release, and stability testing; Drug product in-process, lot release, and stability testing LCP LBI LMN LMS	Approve - Based on Previous History
Amgen Inc. (Referred to as Louisville Distribution Center or LDC) 12000 Plantside Drive , Louisville, KY, United States of America, 40299	3003750095	Master cell bank and working cell bank storage NEC	No Evaluation Necessary

Reviewer's Comment: SATISFACTORY

In the original submission, it was unclear which in-process test(s) the ATO site is responsible for. In its 4/24/20 response to 4/9/20 FDA/IR (Question 1), the applicant clarified that the only drug substance in-process test conducted at ATO is the glycan map method. The glycan map method validation report was included in the original submission in 3.2.R.

FACILITY LEVEL EVALUATION OF DRUG SUBSTANCE MANUFACTURER

Facility name/FEI	ARI / FEI# 3003359885
DMF#	N/A
Any special manufacturing & storage condition?	No
Previous OPMA evaluation (Link)	Relevant and acceptable.
Initial Facility Assessment	
Process experience	Experience manufacturing the proposed DS with no significant process/facility changes
Quality oversight	Recent, relevant 483s with adequate CAPAs proposed
Quality defect signals	No recent BPDRs/FARs/recalls
Data concerns	No unique concerns about batch data
Other Potential Contributing Risk Factors	No additional risk factors identified
704(a)(4) Requests Memo Link:	CMS WA# 323512

Facility Status Assessment: Approve - Based on PLI

The pre-license inspection (PLI) for this drug substance manufacturing facility was performed using the Agency's authority under Section 704(a)(4) of the FD&C Act by requesting records from the manufacturing facility in lieu of performing an on-site inspection. The records request followed the procedures described in the FDA Staff Manual Guide SMG 9004.1, *Policy and Procedures for Requesting Records in Advance of or in Lieu of a Drug Inspection* (Effective Date: August 25, 2017). On 2/21/2020, the Agency requested pre-inspection audit documents in support of the BLA 761140 Rituximab-arrx drug substance manufacturing, testing, and storage site at the ARI facility. On 3/20/2020, the firm submitted the requested documents, which were reviewed and were found acceptable. Items for follow-up on the next GMP surveillance inspection are recommended. The proposed drug substance manufacturing facility is found to be acceptable to support the approval of BLA 761140/0.

The facility was most recently inspected by CDER/OPQ from **4/15-19/2019**. The inspection covered the manufacturing operations for BLA 761086/0 and BLA 761073/0 for drug substances manufacturing of infliximab (ABP 710) and trastuzumab (ABP 980), respectively.

The inspection was conducted in accordance with CPGM 7346.832 and ICH Q7; and covered Quality, Facilities and Equipment, Production, Materials, and Laboratories systems. The inspection was classified as VAI and the BLAs covered were recommended for approval. The firm was previously inspected by CDER/OPQ from 10/29-11/2, 2018. It was conducted to support the review of BLA 761028/03 bevacizumab-awwb (ABP 215) drug substance manufacturing. The inspection was classified as VAI. BLA 761028/0 was recommended for approval. The prior FDA inspection from 7/10-17/2017 was a GMP surveillance inspection and was classified as NAI. The CBI profile was updated and acceptable in FACTS.

The facility is acceptable for the proposed Rituximab-arrx drug substance manufacturing responsibility on the basis of its currently acceptable cGMP compliance status and recent relevant inspectional coverage.

FACILITY LEVEL EVALUATION OF FACILITIES OF OTHER FUNCTIONS

Facility name/FEI	(b) (4)
Facility experience	Inspectional coverage indicates that they have experience with the proposed responsibilities
Quality oversight	Recent, relevant 483s with adequate CAPAs proposed
Data concerns	No unique concerns about data
PLI	No
Facility Status Assessment: Approve - Based on Previous History	
The facility is proposed for the release testing of Residual DNA in DS (LBI). The facility was most recently inspected by FDA from (b) (4). This was a comprehensive GMP Establishment Inspection (EI) of the contract testing laboratory. The inspection was conducted according to CP 7348.808 "Good Laboratory Practice (Nonclinical Laboratories)". The inspection was classified as VAI. The previous inspection was conducted from (b) (4) by Team Biologics in accordance with CP 7345.848 and CP 7356.002. The Quality and Laboratory systems were covered. The inspection was classified as VAI. Profile codes including LBI were updated and acceptable in FACTS. A prior Team Biologics inspection occurred (b) (4). This inspection was classified as NAI. The facility is acceptable for the proposed DS testing responsibility on the basis of its currently acceptable cGMP compliance status and recent relevant inspectional coverage.	
Facility name/FEI	ATO / FEI 2026154
Facility experience	Inspectional coverage indicates that they have experience with the proposed responsibilities
Quality oversight	Recent, relevant 483s with adequate CAPAs proposed
Data concerns	No unique concerns about data
PLI	No
Facility Status Assessment: Approve - Based on Previous History	
The facility is proposed for the drug substance in-process testing, MCB/WCB storage, and WCB manufacture (CBI). The facility was most recently inspected by FDA from 12/9-13/2019 . This was a routine, surveillance cGMP inspection, conducted in accordance with CPGM 7356.002M. System coverage included Quality; Facilities and Equipment; Materials; Production; and Laboratory Controls. The inspection was classified as VAI. Profile CBI was updated and acceptable in FACTS. The previous biennial GMP inspection at this ATO site in April 2017 was classified as NAI. The facility is acceptable for the proposed DS	

responsibilities on the basis of its currently acceptable cGMP compliance status and recent relevant inspectional coverage.

Facility name/FEI	ADL / FEI 3002808497
Facility experience	Inspectional coverage indicates that they have experience with the proposed responsibilities
Quality oversight	No recent 483 observations
Data concerns	No unique concerns about data
PLI	No

Facility Status Assessment: Approve - Based on Previous History

The facility is proposed for the drug substance in-process, lot release, and stability testing (**LBI**). The facility was most recently inspected by FDA from **9/18-20/2019**. This was the first cGMP inspection of a sterile drug manufacturer and contract test laboratory conducted by Team Biologics. The inspection was conducted in accordance with CPGM 7345.848, Inspection of Biological Drug Products (CBER). The quality and laboratory control systems were covered. No FDA 483 was issued during the current inspection. The inspection was classified as NAI. Profile codes including **LBI** were updated and acceptable in FACTS. The facility is acceptable for the proposed DS testing responsibility on the basis of its currently acceptable cGMP compliance status, recent relevant inspectional coverage, and DO recommendation.

S.2.2 Description of the Manufacturing Process and Process Controls

(b) (4)



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Determining When Pre-License/Pre-Approval Inspections are Necessary Inspection Waiver Memorandum

Date: 06/30/2020

From: Amy Devlin, Ph.D., DP Microbiology/Facility Primary Reviewer, OPQ/OPMA/DBM
Maxwell Van Tassell, Ph.D., DP Microbiology 2nd Reviewer, OPQ/OPMA/DBM
Amy Hsu, Ph.D., Product Quality Reviewer, OPQ/OBP/DBRRI
Kristen Nickens, Ph.D., Application Technical Lead, OPQ/OBP/DBRRI

To: BLA File, STN 761140/0

Through: Thuy Thanh Nguyen, Branch Chief, DHSc., OPQ/OPMA/DBM Branch 1

Subject: Pre-License Inspection (PLI) Waiver Memo for Manufacture of ABP 798 Drug Product at (b) (4)

Applicant: Amgen, Inc.

Facility: (b) (4)

Product: RIABNI (ABP 798; rituximab-arrrx)

Dosage: Solution for IV infusion (100 mg/10 mL and 500 mg/50 mL)

Indication: Treatment of adult patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, or pemphigus vulgaris

Waiver Recommendation

Riabni (ABP 798), solution for infusion (100 mg/10 mL and 500 mg/50 mL), drug product (DP) for BLA STN 761140/0 is proposed to be manufactured at (b) (4) DP manufacturing facility (b) (4). The proposed (b) (4) manufacturing process for the ABP 798 DP is similar to that of the licensed process for (b) (4). Based on the firm's compliance history, current acceptable cGMP status, and the (b) (4) manufacture of other licensed products on the same vial-filling line, we recommend that a pre-license inspection of the (b) (4) facility be waived for BLA STN 761140/0.

Summary

BLA STN 761140/0, submitted by Amgen, Inc., provided information and data to support the manufacture of RIABNI, solution for infusion (100 mg/10mL and 500 mg/50mL). The manufacture of ABP 798 drug substance (DS) is performed at Immunex Rhode Island Co. (ARI) facility (FEI: 3003359885). The manufacture of RIABNI DP is carried out at (b) (4) (b) (4). This waiver recommendation is in regard to the DP manufacture at the Baxter facility.

Facility Information

(b) (4)

Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

(b) (4) is a multi-product facility manufacturer that has been licensed to manufacture another licensed product, (b) (4).

2. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The facility was most recently inspected by FDA on (b) (4). This was a PLI in support of BLA (b) (4).

(b) (4) The inspection covered the firm's Quality, Production, Materials, Facilities and Equipment, and Laboratory Controls systems. The inspection team observed the manufacture of (b) (4). A nine-item Form FDA-483 was issued and the inspection was initially classified as potential Official Action Indicated (pOAI). The EIR and the firm's response to form FDA-483, Inspectional Observations were reviewed by CDER/OPMA/DBM (b) (4). The firm's response was deemed adequate and OPMA/DBM recommended approval of the subject BLAs. The inspection was classified as Voluntary Action Indicated (VAI).

The previous FDA inspection from (b) (4), was a routine foreign cGMP surveillance inspection with an evaluation of the firm's Quality, Production, and Laboratory Control systems. A Form FDA 483 was not issued to the firm, and the inspection was classified as No Action Indicated (NAI). Profile codes including SVS were updated and acceptable in FACTS. A prior post-approval inspection was conducted from (b) (4) and classified as VAI.

3. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.*

The same manufacturing areas and similar equipment at (b) (4), licensed for (b) (4) are proposed for RIANBI (ABP 798), solution for infusion (100 mg/10mL and 500 mg/50mL) DP.

4. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

The proposed manufacturing scheme (b) (4) for RIANBI (ABP 798), solution for infusion (100 mg/10mL and 500 mg/50mL) DP is similar with exception of the (b) (4)

Signed:

Amy Devlin, Ph.D.
DP Microbiology/Facility Reviewer, OPQ/OPMA/DBM Branch 1

Maxwell Van Tassell, Ph.D.
2nd DP Microbiology Reviewer, OPQ/OPMA/DBM Branch 1

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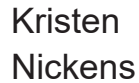
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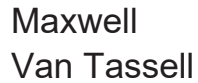
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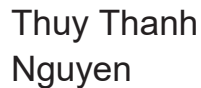
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