CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761106Orig1s000

CHEMISTRY REVIEW(S)

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

LABELS AND LABELING REVIEW

Date of review:	February 26, 2019
Reviewer:	Scott Dallas, RPh, Labeling Reviewer Office of Biotechnology Products (OBP)
Through:	Shadia Zaman, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	761106
Applicant:	Genentech, Inc.
Submission Dates:	May 1 and August 2, 2018; January 10, January 11, February 8, February 11, February 14, February 19, February 22 and February 25, 2019
Product:	Herceptin Hylecta (trastuzumab and hyaluronidase-oysk)
Dosage form(s):	Injection
Strength and Container-Closure:	600 mg and 10,000 units/5 mL (120 mg/2,000 units per mL) single-dose vial
Indication, dose, route, and frequency of administration:	Indicated in adults for the treatment of HER2 overexpressing breast cancer. The dose is 600 mg irrespective of the patient's body weight. No loading dose is required. The dose should be administered subcutaneously over approximately 2 to 5 minutes every three weeks.
Background and Summary Description:	The Applicant submitted an original application seeking approval of trastuzumab and hyaluronidase human injection for subcutaneous injection. Trastuzumab and hyaluronidase human injection has been the subject of pre-Investigational New Drug Application (pre-IND) 109168 sponsored by Genentech, Inc, and is a new dosage form of HERCEPTIN® (trastuzumab) for injection which was approved in the U.S. on September 25, 1998 (BLA 103792).
Recommendations:	The prescribing information, container labels, and carton labeling are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, United States Pharmacopeia (USP) nomenclature and labeling standards, and CDER labeling practices and guidances.

The applicant had proposed to present the "hyaluronidase" portion of the nonproprietary name as "hyaluronidase human" for this combination product. The FDA requested the applicant present the "hyaluronidase" portion of the nonproprietary name without the descriptor "human". The applicant agreed to remove the descriptor "human" from the nonproprietary name. A separate memo discussing this issue will be finalized and uploaded into Panorama, a FDA archival database.

In addition, we note this BLA is a combination product containing two active ingredients. One active ingredient is a specified product, trastuzumab, and the other active ingredient is a non-specified product, hyaluronidase. The specified product, trastuzumab, would be considered the primary active ingredient, so the presentation of the product name on the container and carton labeling will follow the format of a specified product. The combination product, BLA 761064, also presented the product name on the container and carton labeling following the format of a specified product.

The prescribing information, container labels, and carton labeling were reviewed with regard to relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), USP standards, and CDER labeling practices and guidances.

The labels and labeling submitted on February 19 (container and carton) and February 25, 2019 (prescribing information) are acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

(b) (4)

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Appendix B: **Evaluation Tables:**
Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Acceptable
Proper Name (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) *for container of a product capable of bearing a full label* **Comment/Recommendation:** - *Considered a partial label*	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number (21 CFR 610.60) *Considered a partial label* **Comment/Recommendation:** Please include the name of the manufacturer, Genentech, Inc. per 21 CFR 610.60. Consider deletin (b) (4) January 11, 2019: Applicant's response: The manufacturer name has been added to the labe (b) (4) (b) (4) The applicant's revision is acceptable. The label is considered a partial label and only the manufacturer's name must appear on the label.	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) **Comment/Recommendation:** - *Considered a partial label*	☐ No ☒ Yes ☐ N/A
Expiration date (21 CFR 610.60, 21 CFR 201.17) **Comment/Recommendation:** - *Considered a partial label*	☐ No ☒ Yes ☐ 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.

Multiple dose containers (recommended individual dose) 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100 **Comment/Recommendation:** Consider debolding the "Rx Only" statement to allow for prominence of other critical information on the principal display panel. January 11, 2019: Applicant's response: The applicant has removed the bolding from "Rx Only" on the container label to allow for prominence of other critical information on the principal display panel. The applicant's revision is acceptable.	☐ No ☒ Yes ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A
No Package for container 21 CFR 610.60	☒ No ☐ Yes ☐ N/A
Partial label 21 CFR 610.60 21 CFR 201.10 **Comment/Recommendation:** Consider deleting the period punctuation mark after the route of administration, "For Subcutaneous Use Only" and the package type terminology, "Single-Dose Vial". January 11, 2019: Applicant's response: The Applicant agreed to this change. The period punctuation marks after "For Subcutaneous Use Only" and "Single-Dose Vial" have been deleted from the container label. The applicant's revision is acceptable.	☐ No ☒ Yes ☐ N/A
No container label 21 CFR 610.60	☐ No ☐ Yes ☒ N/A

Ferrule and cap overseal	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:
Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).

January 11, 2019: Applicant's response:
The applicant confirmed there is no text on the aluminum seal with plastic flip-off cap and it complies with the revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).

The applicant's revision is acceptable.

Visual inspection 21 CFR 610.60	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:
Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

January 11, 2019: Applicant's response:
The label is placed around the circumference of the vial (refer to Figure 1). A sufficient area of the container remains uncovered for the label's full length or circumference to permit full inspection of the vial contents. The label length is 66 ± 0.2 mm and the vial circumference is 69 ± 0.3 mm leaving a visual area of inspection of 3.0 - 3.5 mm.

The applicant's response is acceptable. The applicant also provided a photo of the vial with a label attached to show the visual inspection area.

NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Route of administration 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
Package type term 21 CFR 201.5	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Please delete the period following the package type term "Single-Dose Vial".

January 11, 2019: Applicant's response:
The Applicant agreed to this change. The period punctuation marks after "For Subcutaneous Use Only" and "Single-Dose Vial" have been deleted from the container label.

The applicant's revision is acceptable.

Drugs **Misleading statements** 21 CFR 201.6	☒ No ☐ Yes ☐ N/A
Strength 21 CFR 201.10 21CFR 201.100	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Please revise the capital letter U in the word Units to appear as a lower case letter u to help prevent any misinterpretation of the strength. Refer to ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations https://www.ismp.org/recommendations/error-prone-abbreviations-list.

January 11, 2019: Applicant's response:
The applicant agreed to this change.

The applicant's revisions are acceptable.

Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Bar code label requirements 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Comment/Recommendation: - *Container label lacks space, then this information must appear on the carton, and PI.*	
Inactive ingredients 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Comment/Recommendation: - *Container label lacks space, then this information must appear on the carton, PI, and IFU (if applicable).*	
Storage requirements	☐ No ☐ Yes ☒ N/A
Comment/Recommendation: - *Container label lacks space, then this information must appear on the carton, PI, and IFU (if applicable).*	
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Package Label[5] Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification 21 CFR 610.61	☐ No ☒ Yes ☐ N/A

[5] 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.

Expiration date 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A
Preservative 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Number of containers 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:
Please revise the capital letter U in the word Units to appear as a lower case letter u to help prevent any misinterpretation of the strength. Refer to ISMP's list of Error-Prone Abbreviations, Symbols, and Dose Designations https://www.ismp.org/recommendations/error-prone-abbreviations-list.

January 11, 2019: Applicant's response:
The applicant revised the capital letter U in the word Units to appear as a lower case letter u to help prevent any misinterpretation of the strength.

The applicant's revisions are acceptable.

Storage temperature/requirements 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Handling: "Do Not Shake", "Do not Freeze" or equivalent (21 CFR 610.61)	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Dr. Zaman confirmed the handling statements of Protect from light, do not shake or freeze.

Multiple dose containers (recommended individual dose) 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Known sensitizing substances	☐ No

21CFR 610.61	☒ Yes ☐ N/A
Inactive ingredients 21 CFR 610.61 21 CFR 201.100 ***Comment/Recommendation:*** USP General Chapter <1091> Labeling of inactive ingredients provides guidance concerning how to alphabetize ingredients. The inactive ingredient has a NF monograph identified by the name Trehalose. Therefore, based upon USP General Chapter <1091> relocate the inactive ingredient α,α-trehalose dihydrate (79.45 mg) to appear after Polysorbate 20 (0.4 mg). January 11, 2019: The applicant's response: The Applicant agreed to this change. The applicant relocated the inactive ingredient α,α-trehalose dihydrate (79.45 mg) to appear after the ingredient Polysorbate 20 (0.4 mg) on the carton label. The applicant's revision is acceptable.	☐ No ☒ Yes ☐ N/A
Source of the product 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Minimum potency of product 21 CFR 610.61 **Comment/Recommendation:** Dr. Zaman confirmed trastuzumab does not have a US standard for potency. Please revise the letters "US" by the proper abbreviation for the United States as "U.S." in the potency statement. January 11, 2019: The applicant's response: The applicant agreed to this change and has revised the letters "US" by the proper abbreviation for the United States as "U.S." on the carton label in the following statements: • In the potency statement from "No US standard of potency." to "No U.S. standard of potency." • On the back panel "US License No. 1048" to "U.S. License No. 1048" The applicant's revisions are acceptable.	☐ No ☒ Yes ☐ N/A
Rx only 21CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Divided manufacturing 21 CFR 610.63	☐ No ☒ Yes ☐ N/A
Distributor 21 CFR 610.64	☐ No ☒ Yes ☐ N/A

Bar code 21 CFR 610.67 21 CFR 201.25	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
Package type term 21 CFR 201.5	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Please delete the period following the package type term "Single-Dose Vial".

January 11, 2019: The applicant's response:
The applicant deleted the period after the package type term.

The applicant's revision is acceptable.

Drugs **Misleading statements** 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement	☐ No

21 CFR 201.55 21 CFR 201.100	☒ Yes ☐ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A
Other	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:
The applicant has proposed labeling for two cartons. The cartons contain 2 different "Made in xx" statements. One statement displays the country as Germany and the other country displays the country as Singapore. The applicant is attempting to comply with the U.S. Customs Borders and Protection (CBP) regulation 19 CFR 134.11., in which applicants are required to include the country of origin on their labeling. OBP Labeling is not responsible for determining the acceptability of these statements per 19 CFR 134.11, but these statements do not interfere with the presentation of the required information under CFR Title 21. Thus, these statements may appear on the carton labeling.

Prescribing Information

Regulations	Acceptable
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Revise the Dosage Forms and Strength statement to read:

Injection: 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) solution in a single-dose vial.

Delete the statemen (b) (4)

January 10, 2019
The applicant revised the statement to be in agreement with the above request, except the applicant revised "hyaluronidase" to read "hyaluronidase human".

Comment to Applicant:
Please delete the word "human" from the nonproprietary name.

February 14, 2019:
The applicant deleted the word "human" from the nonproprietary name.
The applicant's revision is acceptable.

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION
21 CFR 201.57(c)(3)

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Subsection 2.2 Recommended Doses and Schedules

Revise the presentation of the dose from "600 mg" to "600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase)"

Include the statement "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit" per 21 CFR 201.57(c)(3). Insert the statement directly above the subsection titled "Duration of treatment" followed by the statement "Discard any Unused Portion of Tradename in the vial."

Subsection 2.3 Important Dosing Considerations

Revise the presentation of the dose from "600 mg" to "600 mg/10,000 units" (multiple places)

(b) (4)

November 6, 2018: Dr. Shadia Zaman that the data supports stability in syringe at 5°C for up to 48 hours. There is not stability data for 20 – 25°C but the product is stable for up to 8 hours at 30°C, so it would support the micro's statement above. Also the handling conditions of "Protect from light, Do not shake and Do not freeze" are accurate for the DP in the syringe.

After the solution of Tradename is withdrawn from the vial (b) (4) labeled with the peel-off sticke (b) (4) If the syringe containing Tradename is not used immediately, then (b) (4) at room temperature (20 ºC to 25ºC (b) (4) stored refrigerated (2 °C to

8 ºC). Protect from light. Do not shake or freeze.

January 10, 2019:
The applicant added the sentence "Do not use vial if particulates or discoloration is present." This addition is acceptable.

The applicant revised the storage statement to read:
(b) (4) in the refrigerator at 2°C–8°C up to 24 hours and subsequently for 4 hours at room temperature (20°C to 25°C).

January 15, 2019: The storage statement was requested to be further revised to read:
If the syringe containing TRADENAME is not used immediately, then the syringe can be stored in the refrigerator (2°C to 8°C) for up to 24 hours and subsequently at room temperature (20°C to 25°C) for up to 4 hours.

The revised wording above was agreed upon by CMC, Micro and DMEPA.

In addition, wording in the Storage subsection was relocated to appear above the Administration subsection and requested to read:

Prepare the dosing syringe in controlled and validated aseptic conditions. After the solution of TRADENAME is withdrawn from the vial and into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe with the peel-off sticker.

DMEPA found this revision acceptable.

February 8, 2019:
The applicant accepted the revisions recommended above, which were the statements:
If the syringe containing TRADENAME is not used immediately, then the syringe can be stored in the refrigerator (2°C to 8°C) for up to 24 hours and subsequently at room temperature (20°C to 25°C) for up to 4 hours.
And
Prepare the dosing syringe in controlled and validated aseptic conditions. After the solution of TRADENAME is withdrawn from the vial and into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe with the peel-off sticker.

OBP labeling: The presentation of the CMC information in this section is acceptable.

3 DOSAGE FORMS AND STRENGTHS
21 CFR 201.57(c)(4)

☐ No
☒ Yes
☐ N/A

Revise the first sentence to include the identifying characteristics per 21 CFR 201.57(c)(4) to read "Tradename is a colorless to yellowish, clear to opalescent solution for subcutaneous injection:

January 11, 2019:

Dr. Zaman confirmed their overfill specifications meets USP <1151>. Historical data indicated the fill range was (b) (4) mL's.

Dr. Zaman confirmed for the clarity that a "clear to opalescent solution" is accurate. However, the applicant tightened the color description from (b) (4) Thus, it may be more accurate to describe the color as "colorless to pale yellow". A comment will be sent to the applicant.
January 15, 2019:
Please comment if the tightened color specification to (b) (4) in Section 3.2.P.5.1 Specifications necessitates a change in the color description.

February 8, 2019:
The applicant responded that the color description is in line with the specifications in the BLA. The identifying characteristics are acceptable.

11 DESCRIPTION

☐ No
☒ Yes
☐ N/A

(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))
Comment/Recommendation:

USP General Chapter <1091> Labeling of inactive ingredients provides guidance concerning how to alphabetize ingredients. The inactive ingredient has a NF monograph identified by the name Trehalose. Therefore, based upon USP General Chapter <1091> relocate the inactive ingredient α,α-trehalose dihydrate (79.45 mg) to appear after Polysorbate 20 (0.4 mg).

Each mL of solution contains trastuzumab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.39 mg), L-histidine hydrochloride monohydrate (3.67 mg), α,α-trehalose dihydrate (79.45 mg), L-methionine (1.49 mg), polysorbate 20 (0.4 mg), and Water for Injection

Please include the dosage formulation per 21 CFR 201.57(c)(12). Please insert the dosage formulation, injection, directly after the parentheses in the sentence "TRADENAME™ (trastuzumab and hyaluronidase human) is a colorless …" (per LRT and (21 CFR 201.57(c)(12))

June 14, 2018: Dr. Zaman confirmed the qualitative and quantitative information is correct.

November 6, 2018: Dr. Shadia Zaman indicated that the molecular weight for Trastuzumab is 148,220 dalton. Dr. Shen Luo confirmed the hyaluronidase measure of potency is a unit. The "Unit", as the reference standard (RS) used for the potency assay is no longer a USP RS, but an in-house RS.

Dr. Zaman stated the molecular weight of trastuzumab is 148,220 daltons.

January 10, 2019:

The applicant revised the order of the inactive ingredients and added the dosage formulation to the second paragraph. These revisions are acceptable.

January 16, 2019:
However, the applicant deleted the references to the molecular weights.

To Applicant: The molecular weight should be retained for consistency with current labeling practices.

February 8, 2019:
The applicant inserted the molecular weights.
OBP Labeling: The information in this section is acceptable.

February 14, 2019:
The applicant deleted the word "human" from the nonproprietary name.
The applicant's revision is acceptable.

16 HOW SUPPLIED/ STORAGE AND HANDLING
21 CFR 201.57(c)(17)

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

First sentence delet [redacted](b) (4) add identifying characteristics colorless to yellowish, clear to opalescent solution per 21 CFR 201.57(c)(17)

TRADENAME™ (trastuzumab and hyaluronidase human) injection is supplied as a colorless to yellowish, clear to opalescent, sterile, preservative-free solution in a single-dose vial.

Store TRADENAME™ vials in the refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. [redacted](b) (4) to protect from light.

revise to

Store TRADENAME™ vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

Once removed from the refrigerator, TRADENAME™ must be administered within (b) (4) hours and should not be kept above 30°C (86°F).

November 6, 2018: Dr's Madushini Dharmasena and Maria Candauchacon confirmed that the data support the storage of DP "Once removed from the refrigerator, TRADENAME™ must be administered withi (b) (4) hours and should not be kept above 30°C (86°F)." from a microbiology perspective.

November 6, 2018: Dr. Shadia Zaman confirmed the product is stable for up to 8 hours at 30°C. Also the handling conditions for the drug product in the vial "Protect from light, Do not shake and Do not freeze" are accurate. January 16, 2019: A do not shake statement was omitted from this section, so a comment was included for the statement to be added back in the label. February 8, 2019: The applicant accepted the insertion of the "Do not shake" statement. OBP Labeling: The presentation of the CMC information in this section is acceptable.	
MANUFACTURER INFORMATION For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1	☐ No ☒ Yes ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on February 25, 2019)
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- Container Labels (submitted on February 19, 2019)

(b) (4)

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Shadia Zaman

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Date: 2/26/2019 07:40:19AM
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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761106/0**

From: Madushini Dharmasena, Ph.D., DMA Branch IV

Through: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead, DMA Branch IV

Subject: New BLA for the treatment of HER2-positive early breast cancer (EBC) and metastatic breast cancer (MBC)

US License: 1048

Applicant: Genentech

Product: Herceptin Hylecta (Trastuzumab SC)

Dosage: 600 mg and 10,000 Units / 5 mL vial, Subcutaneous injection

Facilities: Roche Parenteral Production Facility, Kaiseraugst, Switzerland (FEI: 146373191)

Receipt Date: 05/01/2018

Action Date: 03/01/2018

Recommendation for Approvability: The drug product (DP) portion of STN 761106/0 was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval.

Review Summary

DP Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	05/01/2018	Original BLA
0005	06/28/2018	Response to information request
0023	11/13/2018	Response to information request
0028	12/11/2018	Response to information request

Genentech, Inc. submitted BLA 761106 to license Trastuzumab SC solution for subcutaneous injection with the proposed proprietary nam (b) (4) for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer. Trastuzumab SC is a co-formulation of Trastuzumab and recombinant human hyaluronidase (rHuPH20). Trastuzumab is a humanized IgG1 k monoclonal antibody directed against HER2. Recombinant human hyaluronidase is a transiently active, locally acting permeation enhancing

enzyme. The mode of action of hyaluronidases is to locally depolymerize the substrate, hyaluronan (hyaluronic acid, HA), at the site of injection in the subcutis, thereby facilitating drug delivery into the systemic circulation. Trastuzumab SC is a new dosage form of HERCEPTIN® (Trastuzumab) injection for intravenous use which was approved in the US on September 25, 1998 (BLA 103792). Trastuzumab SC DP is presented as a solution in glass vials (600 mg/5mL). This application contains CMC information in an eCTD format. This review contains the assessment of the manufacturing process of Trastuzumab SC DP from a sterility assurance and microbiology product quality perspective. The drug substance (DS) review is covered in a separate product quality microbiology review.

1.14 Labeling

The label states that the DP that once removed from the refrigerator, must be administrated withi (b) (4) hours and should not be kept above 30ºC.

Reviewer comment: Since the DP is not reconstituted or diluted, there is no significant risk of microbial contamination. However, the applicant need to update the label as stated in section 3.2.P.2.6.

PENDING

3.2.P DRUG PRODUCT

3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Each single-use, 6 mL vial contains 600 mg of Trastuzumab SC at target pH 5.5 ± 0.3. The composition of Trastuzumab SC DP is listed in table P.3.2-1 (not copied here).

The container closure system for Trastuzumab SC is a (b) (4) glass vial with a rubber stopper, capped and crimped with an aluminum seal fitted with a plastic flip-off cap.

Reviewer comment: The DP composition is adequately described.

SATISFACTORY

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

Reyes Candau-Chacon

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Madushini Dharmasena

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Date: 2/05/2019 11:00:50AM
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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: January 23, 2019

To: Administrative File, **STN 761106**

From: Diane Raccasi, Primary Reviewer, CDER/OPQ/OPF/DMA/Branch IV

Through: Reyes Candau-Chacon, Ph.D. Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV

Subject: New Biologics License Application (BLA) for the treatment of HER-2 positive early breast cancer (EBC) and metastatic breast cancer (MBC)

Applicant: Genentech, Inc.

US License: 1048

Product: (b) (4) (Trastuzumab SC)

Dosage: Single-dose vial containing 120mg/1mL for subcutaneous injection

Indication: Trastuzumab is co-formulated with hyaluronidase for the treatment of patients with epidermal growth factor receptor 2 (HER2) which is overly expressed in breast cancer.

Facilities: Roche Singapore, Pte. Ltd (RSTO) 10 Tuas Bay Link Singapore (FEI 3007164129) Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg Germany (FEI 3002806560)

Receipt Date: April 30, 2018

Action date: February 27, 2018

Recommendation for Approvability: This BLA is recommended for approval from a microbiology product quality perspective.

Review Summary

Genentech has submitted this BLA in order to seek approval of a novel fixed-dose, ready-to use, liquid formulation of trastuzumab for subcutaneous administration for the same breast cancer indications as those currently approved for the intravenous formulation. Trastuzumab SC is provided at a concentration of 600mg/5mL (120mg/mL) and includes recombinant human hyaluronidase (rHuPH20) for efficient delivery.

BLA 761106 was submitted in eCTD on May 1, 2018. This review contains the assessment of the manufacturing process of trastuzumab subcutaneous injection bulk drug substance from a microbiological quality perspective.

Reviewer's comment: The proposed changes in the drug substance manufacturing process to the approved trastuzumab proces (b) (4) (b) (4) *The review of the hyaluronidase drug substance was previously approved and there are no changes to the manufacturing process.*

S. DRUG SUBSTANCE

S.1 General Information

The same antibody, Trastuzumab, is used in the Trastuzuma (b) (4) for intravenous (IV) and subcutaneous administration (SC). (b) (4) (b) (4)

S.2.1 Manufacturer(s)

Roche/Genentech is responsible for the manufacturer, testing and release of Trastuzumab SC. The following sites include the manufacturer, in-process, release testing, stability, and storage of Trastuzumab S (b) (4)

Activity	Name	Address
Manufacturer	Roche Diagnostics GmbH	Nonnenwald 2, 82377 Penzberg Germany
	Roche Singapore	10 Tuas Bay Link Singapore
In-Process Control Testing	(b) (4)	
QC Test and Release		
Stability Testing		
Storage		
Preparation and Storage of Master Cell Bank	Genentech	1 DNA Way, San Francisco, California
Preparation and Storage of Working Cell Bank	Genentech	1 DNA Way, San Francisco, California
	Genentech	1000 New Horizons Way Vacaville, California
Hyaluronidase DS Manufacturer	(b) (4)	

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Diane Raccasi

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Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 1/24/2019 11:37:27AM
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Andrew
Shiber

Digitally signed by Andrew Shiber
Date: 2/05/2019 01:49:58PM
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First Approval for Subcutaneous Administration of Trastuzumab

EXECUTIVE SUMMARY

Recommendation:
BLA: Approval

BLA 761106
Review Number: First round
Review Date: February 1, 2019

Drug Name/Dosage Form	Trastuzumab and hyaluronidase human/solution for injection*
Strength/Potency	600 mg trastuzumab and 10,000 units hyaluronidase per 5ml
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Treatment of patients with HER2-overexpressing (b) (4) breast cancer and HER2-overexpressing metastatic breast cancer
Applicant/Sponsor	Genentech, Inc.

*non-proprietary name under discussion as of date of this review

Product Overview

Trastuzumab and hyaluronidase human solution (non-proprietary name pending; Herceptin Hylecta; Herceptin SC) is a fixed-dose combination of trastuzumab and recombinant human hyaluronidase (rHuPH20) for subcutaneous injection of trastuzumab for the treatment of HER2-overexpressing (b) (4) (b) (4) and metastatic breast cancers. Trastuzumab is an IgG1κ monoclonal antibody that binds to the extracellular domain of HER2, a member of the EGFR family of receptors. Trastuzumab (Herceptin) for intravenous administration (Herceptin IV) was initially approved in the US in 1998 for the treatment of HER2-overexpressing metastatic breast cancers, and subsequently approved for additional indications, including adjuvant treatment of HER2-overexpressing breast cancer. The primary mechanisms of action include inhibition of signaling downstream of HER2 and antibody-dependent cellular cytotoxicity. Herceptin SC was developed to decrease the currently approved administration time of 30-90 minutes for Herceptin IV. The addition of rHuPH20 leads to local depolymerization of hyaluronan, a component of the extracellular matrix of the skin, causing a transient reduction in the hyaluronan viscosity to facilitate the dispersion and absorption of Herceptin. This allows reduction of the trastuzumab administration time to 2-5 minutes for Herceptin SC.

Quality Review Team

Discipline	Reviewer	Office/Division
Drug Substance/Drug Product/Trastuzumab Immunogenicity	Shadia Zaman	OBP/DBRR1
Trastuzumab Immunogenicity Team Lead	Brian Janelsins	OBP/DBRR1
Hyaluronidase; Hyaluronidase Immunogenicity	Shen Luo	OBP/DBRR4
Hyaluronidase; Hyaluronidase Immunogenicity Team Lead	Serge Beaucage	OBP/DBRR4
OBP Labeling	Scott Dallas	OBP IO
Facilities	Marion Michaelis	OPF/DIA
Facilities Team Lead/Branch Chief	Ruth Moore/Zhihao (Peter) Qiu	OPF/DIA
Microbiology Drug Substance	Diane Raccasi	OPF/DMA
Microbiology Drug Product	Madushini Dharmasena	OPF/DMA

Microbiology Quality Assessment Lead	Reyes Candau-Chacon	OPF/DMA
CMC RBPM	Andrew Shiber	OPRO
Application Team Lead	Wendy Weinberg	OBP/DBRR1
OBP Tertiary Reviewer	Kathleen Clouse	OBP/DBRR1

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Amy Tilley	OHOP/DOP1
Signatory Authority	Laleh Amiri-Kordestani	OHOP/DOP1
Cross-disciplinary Team Lead	Jennifer Gao	OHOP/DOP1
Clinical Reviewer -Efficacy	Danielle Krol	OHOP/DOP1
Clinical Reviewer -Safety	Candace Mainor & Yutao Gong	OHOP
Clinical Outcome Assessment (COA)	Yasmin Choudhry / Selena Daniels	OHOP
Nonclinical	Brian Chiu/Tiffany Ricks	OHOP/DHOT
Clinical Pharmacology	Huiming Xia/Pengfei Song	OCP
Clin Pharm Pharmacometrics	Li Fang/Jingyu Yu	OCP
Biostatistics	Laura Fernandes/Shenghui Tang	OB
DOP1 Safety	Kathryn Fedenko and Tiffany Diggs	OHOP/DOP1
DOP1 Labeling	William Pierce	OHOP/DOP1

1. Names:
    a. Proprietary name: Herceptin Hylecta
    b. Trade name: Herceptin Hylecta
    c. Non-proprietary name (proposed): Trastuzumab and hyaluronidase human-xxxx Injection *(note: discussions ongoing at time of this review regarding inclusion of term "human"; suffix to be determined)*
    d. CAS registry number: 180288-69-1
    e. Common name: Herceptin subcutaneous (Herceptin SC)
    f. INN Name (individual components): trastuzumab, vorhyaluronidase alfa
    g. USAN Name (individual components): trastuzumab; hyaluronidase (human recombinant)
    h. OBP systematic name:
    MAB HUMANIZED (IGG1) ANTI P04626 (ERBB2_HUMAN) [RHUMABHER2] AND RPROT P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]

2. Pharmacologic category: Trastuzumab, a therapeutic recombinant humanized monoclonal antibody (IgG1, kappa, anti-HER2), is a HER2/neu receptor antagonist, and recombinant human hyaluronidase is an endoglycosidase used as a dispersing agent

Information requests (OPQ):

Communication	Date
IR # 1 (DMA)	June 20, 2018
IR # 2 (DMA)	July 31, 2018
IR # 3 (OBP-hyaluronidase)	Sept 13, 2018
IR # 4 (OBP-immunogenicity)	Sept 28, 2018
IR # 5 (OBP-hyaluronidase)	Oct 17, 2018
IR # 6 (OBP-DS/DP)	Dec 10, 2018
IR # 7 (DMA)	Dec 11, 2018

IR # 8 (OBP-DS/DP)	Dec 13, 2018
IR # 9 (OBP-immunogenicity)	1/10/2019
IR #10 (OBP-DS/DP)	1/11/2019
IR #11 (OBP-DS/DP)	1/18/2019
IR #12 (OBP-DS/DP)	1/29/2019

Submissions Reviewed (OBP):

Submission(s) Reviewed/(eCTD)	Date Received
761106.0001(1)/original submission	5/1/2018
BLA 103792 (cross-referenced sections, as appropriate)	
BLA 761064 (cross-referenced sections, as appropriate)	
761106.0012(12)/response to IR #3, dated Sept 13, 2018 (hyaluronidase)	9/19/2019
0016 (16)/Clinical Pharmacology Response to IR #4, dated Sept 28, 2018 (immunogenicity)	10/5/2018
761106.0018(18)/response to IR #4 - dated Sept 28,2018 (immunogenicity)	10/12/2018
761106.0019(19)/cross-reference to Rituxan Hycela	10/18/2018
761106.0022(22)/response to IR #5 - dated Oct 17, 2018	10/31/2018
761106.0025(25)/provide missing section 3.2.S.4.5 to Section 3.2.S for hyaluronidase that cross-references the Rituxan Hycela BLA	12/7/2018
761106.0030(30)/response to IR #8 - dated Dec 13, 2018	12/21/2018
761106.0031(29)/ partial response to IR #6 - dated Dec 10, 2018	12/21/2018
761106.35(35)/ response to IR #9 - dated 1/10/2019 (immunogenicity)	1/16/2019
761106.36(36)/response to IR #10 - dated 1/11/2019	1/17/2019
761106.37(37)/partial responses to IR #6 - dated 12/10/2018	1/18/2019
761106.38/updated module 3 in response to IRs dated 12/10,13/2018; 1/11,18/2019	1/24/2019
761106.39(39)/response to IR #11 - dated 1/18/2019	1/25/2019
761106.40/partial response to IR #9 - dated 1/10/2019 (immunogenicity)	1/28/2019
761106.41/response to IR #12 - dated 1/29/2019	2/1/2019

Submissions Reviewed (DMA):

Submission(s) Reviewed	Date Received
761106.0001(1)/original submission	5/1/2018
761106/0005(5)/response to IR #1 - June 20, 2018	6/28/18
761106.0007(7)/ partial response to IR #2 - dated July 31, 2018	8/7/2018
761106.0023(23)/fulfill commitment related to July 31 IR	11/13/2018
761106.0028(28)/response to IR #7 - dated Dec 11, 2018	12/20/2018

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs**:**

DMF#	DMF type	DMF Holder	Item Referenced	Code[1]	Status[2]	Date review completed	Comments (status)
(b) (4)	III		(b) (4)	3	N/A	N/A	None
	V			3	N/A	N/A	None
	III			3	N/A	N/A	none

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

2. Adequate, Adequate with Information Request, Deficient, or N/A (There are enough data in the application; therefore, the DMF did not need to be reviewed.

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

Document	Application Number	Description
Cross-reference to Herceptin BLA (Genentech, Inc.)	BLA 103792	BLA for Herceptin. Herceptin SC drug substance utilizes the same manufacturing as trastuzumab drug substanc (b) (4) (b) (4)
Cross-reference to Herceptin SC preIND	pIND 109168	preIND meeting package and meeting minutes for Herceptin SC
Cross-reference to Rituxan Hycela BLA (Genentech, Inc.)	BLA 761064	BLA for Rituxan Hycela, which contains supporting information for rHuPH20 used in co-formulation with Herceptin
Cross-reference to Hylenex (Hyaluronidase) NDA (Halozyme Therapeutics, Inc.)	NDA 21859	NDA for Hylenex (original approval of the hyaluronidase source used in manufacture of

		Rituxan Hycela and Herceptin SC drug product)

3. Consults: none

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761106 for Herceptin Hylecta (proposed non-proprietary name (pending): Trastuzumab and hyaluronidase human-xxxx/solution for injection) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Herceptin Hylecta is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Summary of Complete Response Issues: none

C. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance
    - Trastuzumab: Roche Diagnostics GmbH, Penzberg, Germany and Roche Singapore Technical Operations
    - Hyaluronidase (b) (4)
  - Drug Product: F. Hoffman-LaRoche Ltd., Kaiseraugst, Switzerland
- Fill size and dosage form
  - 600 mg trastuzumab and 10,000 units hyaluronidase per vial (nominal) in 5 ml for subcutaneous injection
- Dating period:
  - Drug Product: 21 months when stored at 2 to 8 °C
  - Drug Substance:
    - Trastuzumab (b) (4) months when stored a (b) (4)
    - Hyaluronidase (b) (4) months when stored a (b) (4)
  - Stability Option:
    - Not applicable. Data for both drug substance and drug product support the requested dating periods with no further extensions.
- Exempt from lot release
  - Yes
  - Rationale: Specified product in accordance with 21 CFR 601.2a.

D. Benefit/Risk Considerations:

Herceptin Hylecta (non-proprietary name pending; Herceptin SC) is intended for subcutaneous administration of Herceptin for the treatment of HER2-overexpressing early stage and metastatic breast cancers. Herceptin IV is currently licensed and standard of care for these indications; Herceptin Hylecta was developed to shorten the administration time currently approved for Herceptin IV and to increase ease of use and patient convenience and compliance.

The subcutaneous formulation contains a higher protein concentration and the addition of hyaluronidase. The manufacturing process is adequately controlled. Based on extensive analytical characterization, the functional and safety-related attributes of Herceptin Hylecta are

comparable to those of Herceptin. Product quality attributes are adequately controlled, and the immunogenicity assay was deemed suitable to identify any differences in an immune response between subcutaneous and intravenous formulations.

An ongoing multivariate robustness study is underway that was designed to evaluate the impact on product quality of temperature and shipping stresses at differen (b) (4) concentrations at multiple timepoints throughout the DP shelf life. The results of this study will be requested as a PMC for additional support of the control strategies.

E. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

A PMC will be requested to submit the final results of an ongoing formulation robustness/ASTM stress study.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Herceptin for subcutaneous administration (trastuzumab SC) was developed to decrease the currently approved administration time of 30-90 minutes for Herceptin (Herceptin IV). The primary mechanisms of action of both presentations include binding and inhibition of signaling through the HER2/neu receptor, leading to tumor cell growth inhibition, and activation of antibody-dependent cellular cytotoxicity, leading to tumor cell death. (b) (4) (b) (4) (b) (4) Herceptin SC has been approved in the EU since 2013.

The control strategy for Herceptin SC draws on knowledge regarding critical quality attributes, manufacturing process understanding, manufacturing and clinical experience, analytical method understanding, and characterization and stability data. The chemical/physical/biological characteristics of the subcutaneous formulation (Herceptin SC) are well controlled to support product quality of trastuzumab comparable to that of Herceptin IV as relates to safety, purity, potency, and potential for immunogenicity.

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

This table identifies critical quality attributes intrinsic to the API.

CQA (type)	Risk	Origin	Control Strategy	Other notes
Trastuzumab				
HER2 binding	Efficacy	Intrinsic to the	(b) (4)	

(potency)		molecule. Impacted by aggregation, fragmentation, and potentially deamidation. Minimal change is expected during storage through expiry.	(b) (4)	(b) (4)
Inhibition of proliferation (potency)	Efficacy	Intrinsic to the molecule. Impacted by aggregation, fragmentation, isomerization and deamidation. Minimal change is expected during storage through expiry.		
ADCC activity (potency)	Efficacy	Intrinsic to the molecule. Impacted by glycosylation, aggregation, fragmentation, and deamidation. Minimal change is expected during storage through expiry.		ADCC activity was measured at (b) (4) (b) (4) for characterization (S.3).
Identity	Safety and Efficacy	Intrinsic to the molecule		N/A
High Molecular Weight (HMW) species/ Aggregates (product-related impurities)	Efficacy (HER2 binding and ADCC), Safety/ Immunogenicity and potentially PK	Manufacturing process and exposure to heat, light, and pH. Minimal change is expected during storage under recommended conditions through expiry.		The SE-HPLC is validated for the detection of monomer, HMW, and LMW species a (b) (4) (S.4.3) and the method was transferred to (b) (4) HMW species (b) (4)

Fragments (LMW species) (product-related impurities)	Efficacy and PK	Manufacturing process and exposure to heat. Minimal increase in fragments is expected during storage under recommended conditions.	LMW specie
Glycosylation (afucosylated species) (potency)	Efficacy (ADCC activity/FcγRIIIa binding)	(b) (4) No change is expected during downstream manufacturing and storage.	N/A
Glycosylation (high mannose)	PK and efficacy (afucosylated)	(b) (4) No change is expected during downstream manufacturing and storage.	N/A
Deamidation (Asn30) (IE-HPLC Peak 1)	Efficacy	Manufacturing process including hold, storage, and exposure to heat.	Asp-30 is in the Fab portion of trastuzumab. It is assessed to not impact Fc-binding, ADCC, or PK.
Heavy Chain Asp102 isomerization (IE-HPLC Peak 4)	Efficacy	Manufacturing process including hold, storage, and exposure to heat.	IsoAsp-102 is in the Fab portion of trastuzumab.

Sialylated Glycans (potency)	Efficacy: Fc binding and ADCC	(b) (4)	(b) (4) N/A
Terminal Galactosylation (G0, G1, and G2) (potency)	Efficacy: Fc binding and ADCC, perceived to have minimal impact on PK		%G2 correlates with %G1 and inversely correlated with %G0.
NG-HC	Efficacy: Fc binding and ADCC, Nonglycosylated forms do not support ADCC.		
Methionine (Met255) oxidation	PK	No manufacturing process parameters were identified in this application to impact levels of oxidized Met255.	(b) (4)
Met431 oxidation	PK	No manufacturing process parameters were identified in this application to impact levels of oxidized Met431.	
Protein Content (mg/mL)	Efficacy	Manufacturing process	N/A
Hyaluronidase (rHuPH20) *(adapted from ATL memo, BLA 761064 with input from hyaluronidase primary reviewer)*			
Enzymatic activity	Impact on		(b) (4)

(potency)	trastuzumab distribution, PK	(b) (4)
Aggregates (purity)	Efficacy (MOA); immunogenicity	(b) (4)
Oxidized species (purity)	Efficacy (MOA)- impact on enzymatic activity when both met residues are oxidized	
Hydrolyzed species (purity)	Efficacy (MOA)- impact on enzymatic activity	
Primary Sequence	Impact on trastuzumab distribution, PK and immunogenicity	Expression construct and cell line
Oligosaccharide profile	Efficacy (MOA)- impact on enzymatic activity	(b) (4)

B. Drug Substance [Trastuzumab] Quality Summary

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

The following table presents CQAs derived from the drug substance manufacturing process and general drug substance attributes.

Category (type)	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	(b) (4)	(b) (4)	
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity HCPs enzymes contribute to (b) (4)	Production cell line		Table S.2.5-10 shows CHOP (b) (4) process in process validation. (b) (4)
Host Cell DNA (process-related impurity)	Safety	Production cell line		Table S.2.5-11 shows DNA (b) (4) (b) (4)
(b) (4) (process-related impurity)	Safety and Immunogenicity	Process related impurit (b) (4) (b) (4)		Table S.2.5-12 show (b) (4) (b) (4) (b) (4) in process validation. (b) (4)
(b) (4) (process-related impurity)	Safety, immunogenicity	Cell bank cryopreservation medium or culture medium		Removal of these impurities are described in BLA 103792 (cross-referenced).
Viruses (contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations.		Information is provided in BLA 103792.
Mycoplasma (contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture		Information is provided in BLA 103792.

		operations.	(b) (4)	
Leachables (process-related impurity)	Safety	Manufacturing components and the DS container closure system		
Bacterial Endotoxins	Safety, Purity	Raw materials and manufacturing process		
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process		

- Description (trastuzumab):
  Trastuzumab is a humanized IgG1 kappa monoclonal antibody with a molecular weight of 148,220 daltons. It contains human framework regions with the complementarity-determining regions of a murine antibody that binds to the extracellular domain of HER2. It is comprised of two 449-residue heavy chains and two 214-residue light chains that are covalently linked by interchain disulfide bonds. Trastuzumab harbors one glycosylation site at an asparagine position (Asn300) that is conserved in human IgG1 type antibody heavy chains.

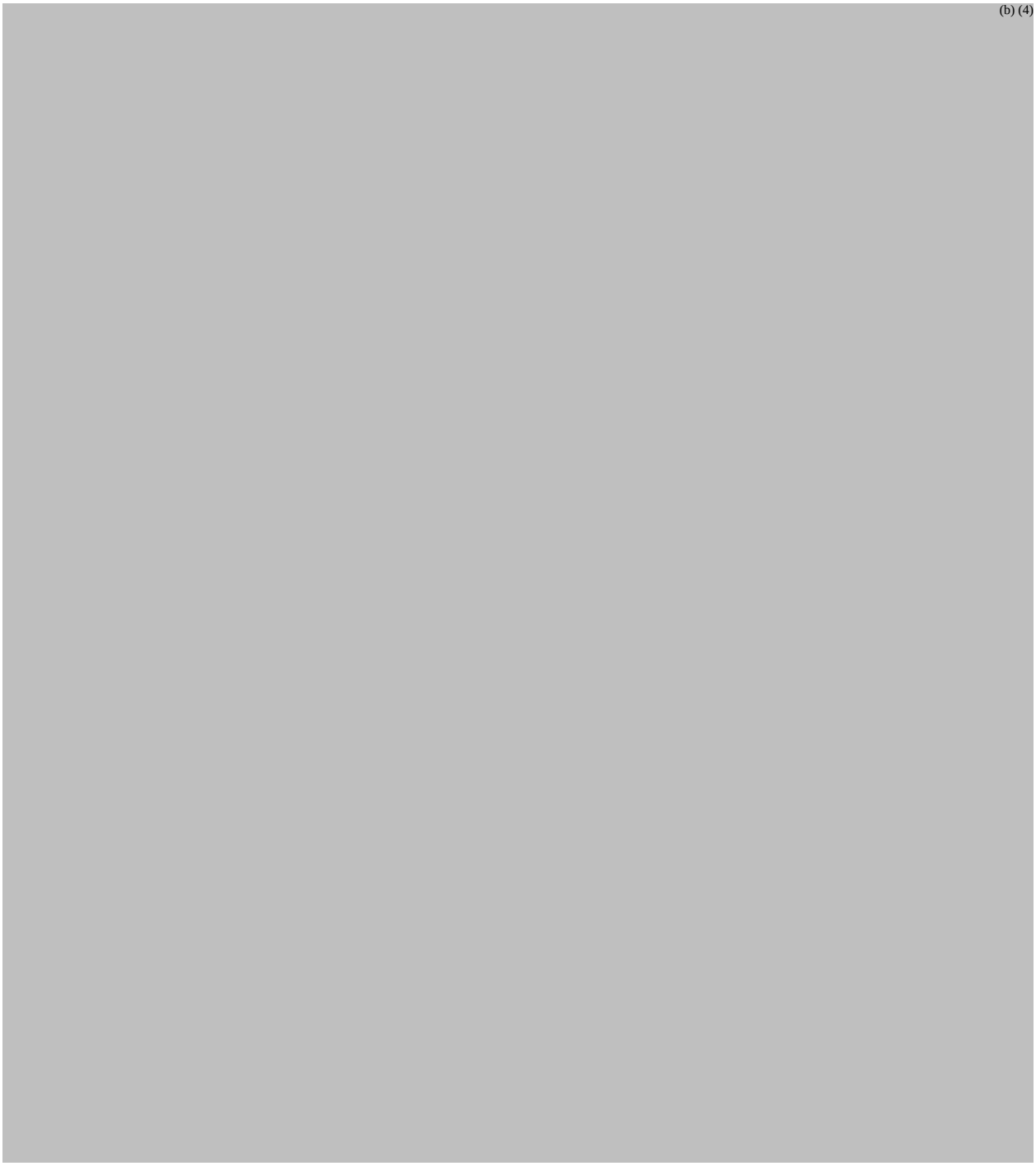
- Mechanism of Action (MoA):
  The clinical efficacy of trastuzumab is believed to be mediated via two major mechanisms. As a primary mechanism of action, trastuzumab selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2, and blocks downstream signaling through this receptor, thereby inhibiting cell proliferation. Trastuzumab also engages cells of the immune system through its Fc domain to mediate antibody dependent cellular cytotoxicity (ADCC). Complement-dependent cytotoxicity is not believed to contribute to the mechanism of action of trastuzumab.

- Potency Assay:
  Potency of Herceptin SC DS and DP is assessed using a quantitative in vitro bioassay that measures the anti-proliferative effects of trastuzumab binding to the HER2

expressing breast ductal carcinoma cell line, BT-474. Trastuzumab binds to amino acids 529-627 of the extracellular domain of HER2 and blocks downstream signaling. Inhibition of proliferation is measured by changes in color and fluorescence of the redox dye alamarBlue, which is blue and non-fluorescent in its oxidized state. When taken up by live cells, intracellular metabolic reduction converts it into a red product that is highly fluorescent. A dose-response curve generated for the samples and RS provides the basis for quantitation.

- Reference Materials:

(b) (4)



(b) (4)

C. Drug Substance [Hyaluronidase] Quality Summary *(adapted from ATL memo of cross-referenced BLA 761064 with input from hyaluronidase primary reviewer)*

Table 3: Drug Substance (Hylauronidase) CQA Process Risk Identification and Lifecycle Knowledge Management.

Category (type)	Risk	Origin	Control Strategy	Other
Visual appearance (general)	safety and immunogenicity	May be affected by cell culture, purification and (b) (4) steps	(b) (4)	
Protein quantity (general)	efficacy	DS manufacture (b) (4)		
Host cell proteins (process impurity)	safety and immunogenicity	Cell culture		(b) (4)
DNA (process impurity)	safety and immunogenicity	Cell culture		
(b) (4) (process impurity)	safety	Cell culture		
(b) (4) (process impurity)	safety, immunogenicity, and allergenicity	Cell culture		
(b) (4) (process impurity)	safety	Cell culture		
(b) (4) (process impurity)	safety	Cell culture		
(b) (4) (process	safety	(b) (4)		

impurity)		(b) (4)	(b) (4)	(b) (4)
(b) (4) (process impurity)	safety			
(b) (4) (process impurity)	safety			
Endotoxin (contaminant)	safety and purity	Raw materials and manufacturing process		
Bioburden (contaminant)	Safety, purity and efficacy due to degradation or modification of the product by contaminating organism	Raw materials and manufacturing process		

- Description (hyaluronidase, recombinant human):

Recombinant human hyaluronidase (rHuPH20, RPROT P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]) is a glycosylated single chain protein with 447 amino acids. The calculated molecular weight of the full-length polypeptide is 51,106 Da. Glycosylation increases the molecular weight to 60,000-65,000 Da. There are six N-linked and one O-linked glycosylation sites.
Note that rHuPH20 is approved as HYLENEX as a 505(b)(2) NDA.

- Mechanism of action:

rHuPH20 depolymerizes hyaluronan under physiological conditions and acts as a spreading factor in vivo that facilitates the dispersion and absorption of trastuzumab by temporarily clearing a path through the connective tissue in the subcutaneous space.

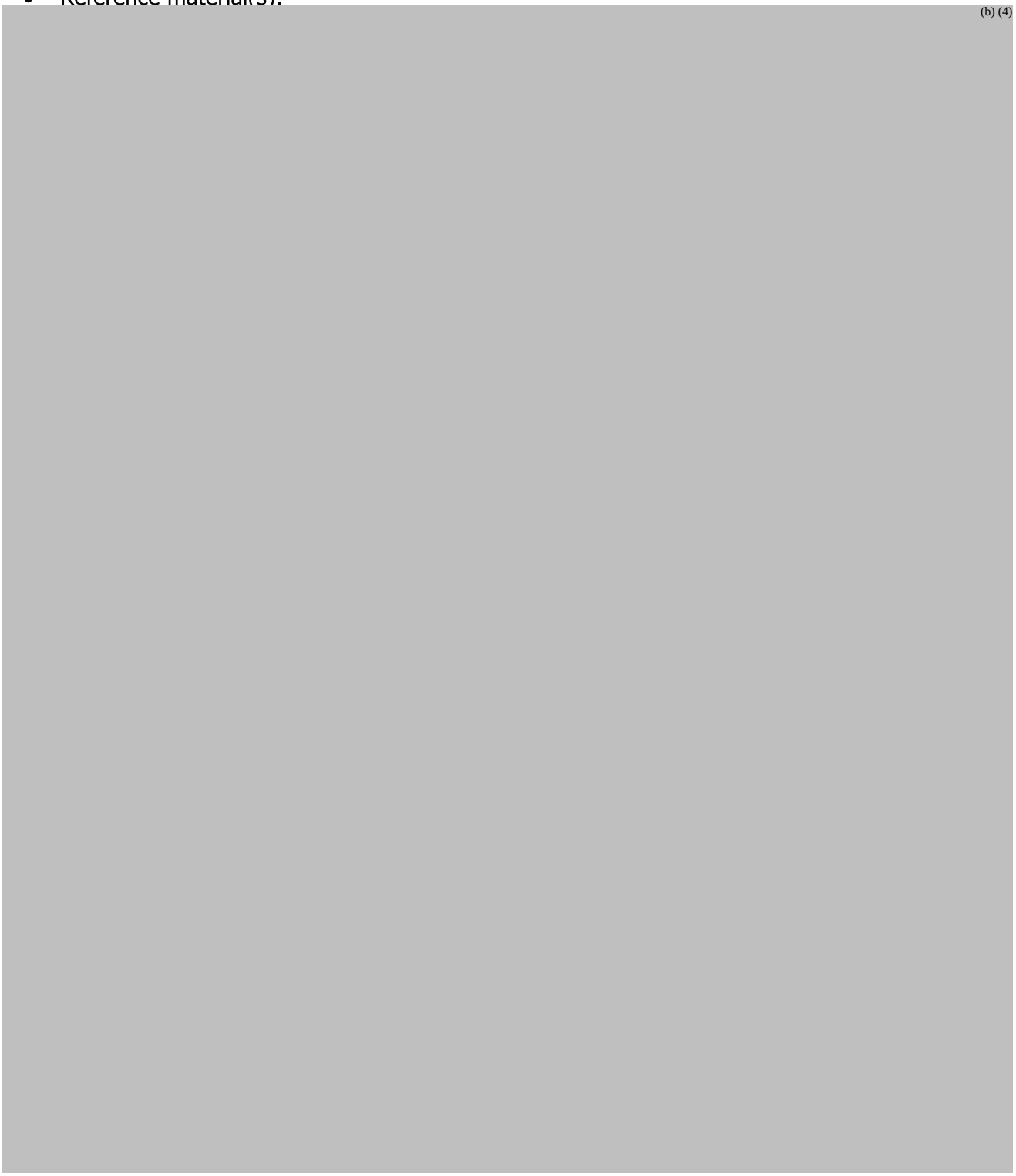
- Potency Assay:

Enzymatic activity is measured with a turbidimetric assay where an insoluble precipitate is formed when hyaluronic acid binds with a cationic precipitant. rHuPH20 is incubated with hyaluronan substrate for 30 minutes and the undigested hyaluronan is precipitated upon the addition of cetylpyridinium chloride. Turbidity is measured at 640 nm and the decrease

in turbidity resulting from enzyme activity on the hyaluronan substrate is a measure of the enzyme activity. This is a plate-based method that is a modification of the USP monograph for Hyaluronidase for Injection (animal extracted hyaluronidase).

- Reference material(s):

(b) (4)



(b) (4)

[redacted]

D. Drug Product [Herceptin Hylecta] Quality Summary:

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

The following table 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.

CQA (type)	Risk	Origin	Control Strategy	Other
Color of solution	Safety and efficacy	Formulation, contamination, or degradation	(b) (4) [redacted]	
Clarity, opalescence of solution (general)	Safety and efficacy	Formulation, contamination, or degradation		
Protein concentration (trastuzumab)	Efficacy	DP manufacture		
Protein concentration (hyaluronidase)	Efficacy	DP manufacture		
Osmolality	Efficacy	DS manufacture and compounding		
pH	Safety and Efficacy	Formulation		N/A
Protein Content	Efficacy	Manufacturing process		N/A
Polysorbate 20	Safety and Efficacy (b) (4) [redacted]	Formulation		N/A
Particulate matter (visible and subvisible) (Product or process related impurities)	Safety/immunogenicity	Manufacturing process and container closure system		N/A
Deliverable content (general)	Efficacy/dosing	Manufacturing process		N/A

			(b) (4)	
Leachables (process related impurities)	Safety	Manufacturing equipment and container closure		N/A
Sterility (contaminant)	Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process		None
Endotoxin (contaminant)	Safety and purity	Contamination may be introduced from the raw materials or throughout the DP manufacturing process		Provides a 28-fold safety factor.
Container closure integrity	Safety	Container closure breaches during storage. May be impacted by storage conditions.		None

- Potency and Strength:
  120 mg trastuzumab/2,000 Units hyaluronidase per mL

- Summary of Product Design:
  Herceptin Hylecta is supplied as 600 mg trastuzumab and 10,000 units hyaluronidase human per 5 mL in single-dose vials. Each mL of solution contains trastuzumab (120 mg), hyaluronidase human (2,000 units), L-histidine (0.39 mg), L-histidine hydrochloride monohydrate (3.67 mg), L-methionine (1.49 mg), polysorbate 20 (0.4 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

- List of Excipients: L-Histidine/L-Histidine Hydrochloride Monohydrate, L-Methionine, α,α-Trehalose Dihydrate, Polysorbate 20. Except for L-Methionine, all excipients are compendial.

- Reference Materials:

(b) (4)

(b) (4)

- Container closure:
  The Trastuzumab SC DP container closure system consists of Colorless 6 mL (b) (4) glass via (b) (4) rubber (b) (4) stopper, and aluminum seal with plastic flip-off cap.

- Dating period and storage conditions:
  21 months for trastuzumab/hyaluronidase drug product (600 mg trastuzumab/10,000 units hyaluronidase per vial) when stored at 5°C (2 to 8°C).

- List of co-package components, if applicable: N/A

E. Novel Approaches/Precedents: Herceptin Hylecta is considered a fixed-dose combination product with two active ingredients: trastuzumab as the API with activity against HER2-overexpressing breast cancers, and rHuPH20, recombinant human hyaluronidase, to increase the dispersion and absorption of trastuzumab when administered subcutaneously.

F. Any Special Product Quality Labeling Recommendations: none

G. Establishment Information:

Overall recommendation: *Approve*					
DRUG SUBSTANCE for trastuzumab SC					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
trastuzumab: Virus, Mycoplasma & Leptospira testing. Also, cell bank preparation and storage. rHuPH20: Leptospira testing	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 USA	080129000/ 2917293	Inspection waived	N/A	Approve based on inspection and compliance history
trastuzumab: Manufacturing and testing. Also, cell bank storage.	Roche Singapore Technical Operations Pte. Ltd (RSTO), 10 Tuas Bay Link,	937189173/ 3007164129	Inspection waived	N/A	Approve based on inspection and compliance history

	Singapore, 637394				
trastuzumab: Virus and Leptospira testing rHuPH20: Leptospira testing	Genentech, Inc. 1 Antibody Way Oceanside, CA 92056-5802 USA	146373191/ 3006129086	Inspection waived	N/A	Approve based on inspection and compliance history
trastuzumab: Cell Bank Storage	Genentech 1000 New Horizons Way Vacaville, CA 95688-9431	004074162/ 3002902534	Inspection waived	N/A	Approve based on inspection and compliance history
trastuzumab: Manufacturing and testing. Also, storage and preparation of cell banks. rHuPH20: Leptospira testing	(b) (4)		Inspection waived	N/A	Approve based on inspection and compliance history
trastuzumab: Bioassay testing			Inspection waived	N/A	Approve based on inspection and compliance history
trastuzumab: Storage rHuPH20: Storage			Inspection waived	N/A	Approve based on inspection and compliance history
trastuzumab: Virus testing			Inspection waived	N/A	Approve based on inspection and compliance history
rHuPH20: Manufacturing, Testing and Labeling			Inspection waived	N/A	Approve based on inspection and compliance history
rHuPH20: Release Testing (residual DNA)			Inspection waived	N/A	Approve based on inspection and compliance history
rHuPH20:			Inspection waived	N/A	Approve based on

Mycoplasma testing, viral in-vitro testing, cell bank manufacture and storage.	(b) (4)				inspection and compliance history
rHuPH20: Oligosaccharide analysis and enzymatic activity assay.			Inspection waived	N/A	Approve based on inspection and compliance history
rHuPH20: Storage and Distribution			Inspection waived	N/A	Approve based on inspection and compliance history
rHuPH20: Release responsibilities, no manufacturing or testing.	Halozyme Therapeutics, Inc. 11388 Sorrento Valley Road San Diego, CA 92121	026077359/ 3004946494	N/A	N/A	No Further Evaluation
DRUG PRODUCT for trastuzumab SC					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
trastuzumab SC: Manufacturing, testing, packaging and labeling.	F. Hoffmann-La Roche, Ltd Wurmisweg Kaiseraugst, Switzerland CH-4303	485244961/ 3003973536	Inspection waived	N/A	Approve based on inspection and compliance history

H. Facilities: no approvability issues

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
Post-approval annual stability protocol
ii. Outstanding review issues/residual risk: N/A
iii. Future inspection points to consider: N/A

b. Drug Product

i. Protocols approved:
Post-approval annual stability protocol

ii. Outstanding review issues/residual risk: A PMC will be requested to submit the final results of an ongoing formulation robustness/ASTM stress study to support stability on shipping conditions

iii. Future inspection points to consider:

1. Leachable study (described in Section 3.2.S.6.2.1) is ongoing for storage of three drug substance batches, (b) (4) (b) (4) These batches will be analyzed for volatile, organic species and elemental impuritie (b) (4) (b) (4) Review updates on this study during inspection.

2. Review their visual inspection of vials procedure (b) (4) (b) (4)

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/source material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/source material		X		
7.	Non-Mammalian Cell Substrate/Source Material			X	
8.	Transgenic Animal source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity			X	
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]				X
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)		X		
17.	End of Phase II/Pre-NDA Agreements tem			X	
18.	SPOTS (special products on-line tracking system)				X
19.	USAN assigned name				
20.	Other [fill in]				X
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other			X
26.	Other QbD Elements – Design of experiments		X		
27.	Real Time release testing (RTRT)			X	
28.	Parametric release in lieu of Sterility testing			X	
29.	Alternative Microbiological test methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipient (b) (4)	X		
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}				X

Kathleen Clouse Strebel

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Reyes Candau-Chacon

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Zhihao Peter Qiu

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Wendy Weinberg

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BLA STN 761106
Product: Herceptin Hylecta (Trastuzumab and Hyaluronidase)
Manufacturer: Genentech

OBP CMC Review Data Sheet

1. BLA#: 761106

2. Review Date: 2/1/19

3. Primary Review Team:

a. Medical Officer:	Jennifer J Gao, Laleh Amiri Kordestani (TL) (efficacy)
b. Pharm/Tox:	Haw-Jyh Chiu
c. Product Quality Team:	Shadia Zaman (DBRR1, DS/DP/immunogenicity), Shen Luo (DBRR4, hyaluronidase), Serge Beaucage (DBRR4, hyaluronidase TL), Brian Janelsins (DBRR1, immunogenicity TL), Madushini Dharmasena (DP) and Diane Raccasi (DS) (DMA), Reyes Candau-Chacon (DMA TL)
d. Facilities:	Marion Michaelis (DIA)
e. Clinical Pharmacology:	Huiming Xia
f. Statistics:	Laura Fernandes
g. OBP Labeling:	Scott Dallas
h. RBPM:	Andrew J. Shiber (CMC), Amy Tilley (Clinical)

4. Major GRMP Deadlines:

a. Filing Meeting:	June 15, 2018
b. Mid-cycle meeting:	October 15, 2018
c. Wrap-up meeting:	January 25, 2019
d. Primary review due:	January 23, 2019 (including Secondary Review Sign-off)
e. Secondary review due:	February 1, 2019 (when needed)
f. PDUFA action date:	March 1, 2019

5. Communications with Sponsor and OND:

Communication/Document:	Date
Information Request #1 for Immunogenicity	9/28/18
Information Request #2 for DS	12/10/18
Information Request #3 for DP	12/13/18
Information Request #4 for Immunogenicity	1/10/19
Information Request #5 for DS and DP	1/11/19
Information Request #6 for DS and DP	1/18/19
Information Request #7 for DS and DP	1/29/19

6. Submission Reviewed:

Submission reviewed /sequence number	Date Received	Review Completed (yes or no)
STN 761106/16 (Response to IR #1)	10/5/18	yes
STN 761106/18 (Response to IR #1)	10/12/18	yes
STN 761106/30 (Response to IR #3)	12/21/18	yes
STN 761106/31 (Response to IR #2)	12/21/18	yes

STN 761106/35 (Response to IR #4)	1/16/19	yes
STN 761106/36 (Response to IR #5)	1/17/19	yes
STN 761106/37 (Response to IR #2)	1/18/19	yes
STN 761106/38 (Response to IR #2)	1/24/19	yes
STN 761106/39 (Response to IR #6)	1/25/19	yes
STN 761106/40 (Response to IR #4)	1/28/19	yes
STN 761106/41 (Response to IR #7)	2/1/19	yes

7. Drug Product Name/Code/Type:
   - a. Proprietary Name: Herceptin Hylecta
   - b. Trade Name: Herceptin Hylecta
   - c. Non-Proprietary Name/USAN: Trastuzumab and hyaluronidase human-xxxx Injection (note: discussions ongoing at time of this review regarding inclusion of term "human")
   - d. CAS Name: 180288-69-1
   - e. Common Name: Herceptin subcutaneous (Herceptin SC)
   - f. INN Name (individual components): Trastuzumab, Vorhyaluronidase Alfa
   - g. Compendial Name: N/A
   - h. OBP systematic name: COMBINATION: MAB HUMANIZED (IGG1) ANTI P04626 (ERBB2_HUMAN) [RHUMABHER2] AND RPROT P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]
   - i. Other names: rhuMAb HER2 or anti-HER2 for trastuzumab, rHuPH20 for hyaluronidase

8. Pharmacological Category: Trastuzumab is a HER2/neu receptor antagonist, and hyaluronidase is an endoglycosidase.

9. Dosage Form: 600 mg trastuzumab and 10,000 Units hyaluronidase in 5 mL vial

10. Strength/Potency:
    (i) The concentration/strength of the Drug Product: 120 mg trastuzumab/2,000 Units hyaluronidase per mL
    (ii) Type of potency assay(s): Anti-proliferation assay for trastuzumab and enzymatic activity assay for hyaluronidase

11. Route of Administration: Subcutaneous Injection

12. Related/Supporting Documents:

A. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
		(b) (4)	Yes	None
			Yes	None

(b) (4)	Yes	None

B. Cross-referenced applications:

Document	Application Number	Description
Cross reference to other GNE application	BLA 761064	BLA for Rituxan HYCELA
Cross reference to other GNE application	BLA 103792	BLA for trastuzumab v1.1, which is the same manufacturing process as trastuzumab SC v1. (b) (4) (b) (4)

13. Inspectional Activities: none (waived)

14. Consults Requested by OBP: none for trastuzumab

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
	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents:
The BLA describes trastuzumab co-formulated with recombinant human hyaluronidase for subcutaneous administration. Hyaluronidase acts as a tissue dispersion agent to facilitate the subcutaneous administration of 600 mg trastuzumab in 5 mL for HER2-overexpressing breast cancer patients in about 2-5 minutes as opposed to about 30 – 90 minutes that may be needed for intravenous administration of trastuzumab.

A similar approach was used to develop another product manufactured by the same sponsor, named Rituxan Hycela (co-formulation of rituximab and recombinant human hyaluronidase for subcutaneous administration of rituximab), which was approved by CDER in 2017 under BLA 761064. As with the present product, both the antibody and the enzyme are considered active ingredients in that BLA. The ratios of concentrations of the mAb (120 mg/mL) and hyaluronidase (2,000 units/mL) in both products are the same. However, the dosages of Rituxan Hycela are 11.7 mL and 13.4 mL for different indications, higher than the dosage of 5 mL for trastuzumab SC.

Hyaluronidase drug substance used for trastuzumab SC formulation is produced by the same manufacturer using the same process approved under BLA 761064. Because of this, in a CMC pre-BLA

meeting held on November 17, 2017, the agency agreed that the sponsor can cross-reference Module 3 sections in the currently approved BLA 761064 dossier for hyaluronidase drug substance information.

Trastuzumab drug substance used in trastuzumab subcutaneous (SC) formulation is the same active pharmaceutical ingredient that is used in trastuzumab drug product (Herceptin) for intravenous administration. However, trastuzumab SC is formulated at a higher concentration of 120 mg/mL in the subcutaneously administered drug product compared to the reconstituted concentration of 21 mg/mL of the lyophilized product used for intravenous administration of Herceptin drug product described in BLA 103792. Trastuzumab SC is produced by the same manufacturer and uses the same drug substance manufacturing process as Hercepti (b) (4) (b) (4) therefore, the sponsor has cross-referenced Module 3 sections in the currently approved BLA 103792 for trastuzumab drug substance.

17. Administrative: N/A

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 761106 for Herceptin HYLECTA manufactured by Genentech. The data submitted in this application are adequate to support the conclusion that the manufacture of Herceptin HYLECTA is well controlled and leads to a product that is pure and potent. We recommend that Herceptin HYLECTA be approved for human use under the conditions specified in the package insert.

We recommend an expiration dating period o (b) (4) months for trastuzumab drug substance when stored a (b) (4)

We recommend an expiration dating period of 21 months for trastuzumab/hyaluronidase drug product (600 mg trastuzumab/10,000 units hyaluronidase per vial) when stored at 5°C (2 to 8°C).

We recommend approval of the proposed release and shelf life specifications for trastuzumab drug substance, hyaluronidase drug substance, and trastuzumab/hyaluronidase drug product.

II. List of Deficiencies to be Communicated

None

III. List of Post-Marketing Commitments/Requirements

Formulation Robustness at Varying (b) (4) Concentrations

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The claim for categorical exemption is accepted.

V. Primary Container Labeling Review
Refer to a separate review memo authored by Scott Dallas, the OBP labeling reviewer.

VI. Review of Common Technical Document- Quality Module 3.2
The review of Module 3.2 for trastuzumab SC drug substance and drug product are reviewed below in order of the Table of Contents below. The review of Module 3.2 for vorhyaluronidase alfa will be completed by Shen Luo in a separate memo. The review of Module 5.3.1.4 for immunogenicity for trastuzumab will be provided in a separate memo.

Figures and tables are copied from the submission unless otherwise indicated.

Table of Contents

Reference ID: 4399882

Description of Drug Substance and Drug Product

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Reference ID: 4399882

Shadia Zaman

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Wendy Weinberg

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