

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761081Orig1s000

OTHER REVIEW(S)



U.S. FOOD & DRUG
ADMINISTRATION

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

LABELS AND LABELING REVIEW

Date of review:	February 5, 2019
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Lymarie Maldonado-Baez, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761081
Applicant:	Pfizer Ireland Pharmaceuticals
Submission Date:	September 28, 2018
Product:	Trazimera (trastuzumab-qyyp)
Dosage form(s):	For injection
Strength and Container-Closure:	420 mg/vial in a multiple dose vial
Purpose of review:	The Applicant submitted a biologics license application for Agency review as a proposed biosimilar to US-licensed Herceptin.
Recommendations:	The prescribing information (submitted on February 5, 2019), container labels and carton labeling (submitted on January 29, 2019), and Bacteriostatic Water for Injection Container Label (submitted on December 28, 2018) were reviewed and found to be acceptable (see Appendix C) 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

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B). The prescribing information, container labels, and carton labeling were reviewed and found to comply with 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, 21 CFR 208.20(a)(7), 21 CFR 208.20(a)(7)).

The prescribing information (submitted on February 5, 2019), container labels and carton labeling (submitted on January 29, 2019), and Bacteriostatic Water for Injection container label (submitted on December 28, 2018) were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on September 28, 2018)

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Container Labels (submitted on December 28, 2018)

(b) (4)

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Proper Name <i>(for container of a product capable of bearing a full label)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices: placement of dosage form below the proper name</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Comment/Recommendation: Ensure that the approved four-letter suffix is applied to the proper name. <i>The applicant revised as requested.</i>	
Manufacturer name, address, and license number <i>(for container of a product capable of bearing a full label)</i>	Acceptable
21 CFR 610.60 (a)(2), 21 CFR 201, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Comment/Recommendation: Per 21 CFR 610.60 (a)(2), the name address and license number of the manufacturer shall appear on the container label. Add the manufacturer's address to the container label as follows: Mfg. by Pfizer Ireland Pharmaceuticals Cork, Ireland US License No. 2060 <i>The applicant revised as requested.</i>	
<i>Recommended labeling practices (using the following qualifying statement "Manufactured by:")</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Lot number or other lot identification <i>(container capable of bearing a full label shall bear)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Expiration date <i>(container capable of bearing a full label shall bear)</i>	Acceptable

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.

21 CFR 610.60, 21 CFR 201.17	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices (the expiration date appears on all aspects of the package):</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Product Strength</u>	<u>Acceptable</u>
21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices: expression of strength for injectable drugs Reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176 USP General Chapters: <7> Labeling</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Multiple dose containers (recommended individual dose)</u>	<u>Acceptable</u>
21 CFR 610.60, 21 CFR 201.55	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Statement: "Rx only"</u>	<u>Acceptable</u>
21 CFR 610.60, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Recommended labeling practices: prominence of Rx Only	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Medication Guide</u>	<u>Acceptable</u>
21 CFR 610.60, 21 CFR 208.24	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>No Package for container</u>	<u>Acceptable</u>
21 CFR 610.60	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Proper Name (for container bearing a partial label)</u>	<u>Acceptable</u>
21 CFR 610.60, 21 CFR 201.10	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Manufacturer name, address, and license number (for container bearing a partial label)</u>	<u>Acceptable</u>
21 CFR 610.60, 21 CFR 201.10	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

Recommended labeling practices: <i>U.S license number for container bearing a partial label</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Lot number or other lot identification</u> <i>(for container bearing a partial label)</i>	<u>Acceptable</u>
21 CFR 610.60, 21 CFR 201.10	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Expiration date</u> <i>(for container bearing a partial label)</i>	<u>Acceptable</u>
21 CFR 201.17	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>No container label</u>	<u>Acceptable</u>
21 CFR 610.60	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Ferrule and cap overseal</u> <i>(for vials only)</i>	<u>Acceptable</u>
<i>Recommended labeling practices: United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i> Comment/Recommendation: <i>Applicant's response: The Applicant confirms that no text or other markings are present on the ferrule and cap overseal of the vials.</i> <i>We find the applicant's response acceptable</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Visual inspection</u> <i>(for vials only)</i>	<u>Acceptable</u>
21 CFR 610.60(e)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

Comment/Recommendation:

Applicant's response: The Applicant confirms there is sufficient area on the container to allow for visual inspection both around the circumference and full length of the vials. See Figure 1: Mock up 420 mg Drug Product Vial and Figure 2: Mock-up Diluent Vial.

(b) (4)

<u>NDC numbers</u>	<u>Acceptable</u>
21 CFR 201.2, 21 CFR 207.35	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Route of administration</u>	<u>Acceptable</u>
21 CFR 201.5, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Recommended labeling practices: route of administration statement to appear after the strength statement on the principal display panel	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Preparation instructions</u>	<u>Acceptable</u>
21 CFR 201.5	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Package type term</u>	<u>Acceptable</u>
<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. USP chapter <659> Packaging and Storage Requirements</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Misleading statements</u>	<u>Acceptable</u>
21 CFR 201.6	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Prominence of required label statements</u>	<u>Acceptable</u>
21 CFR 201.15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Spanish-language (Drugs)</u>	<u>Acceptable</u>
21 CFR 201.16	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u>	<u>Acceptable</u>
21 CFR 201.20	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Phenylalanine as a component of aspartame</u>	<u>Acceptable</u>
21 CFR 201.21	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Sulfites; required warning statements</u>	<u>Acceptable</u>
21 CFR 201.22	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Bar code label requirements</u>	<u>Acceptable</u>
21 CFR 201.25, 21 CFR 610.67	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 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>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u>	<u>Acceptable</u>

21 CFR 610.68, 21 CFR 201.26	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Net quantity</u>	<u>Acceptable</u>
21 CFR 201.51	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Usual dosage statement</u>	<u>Acceptable</u>
21 CFR 201.55, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Inactive ingredients</u>	<u>Acceptable</u>
21 CFR 201.100	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Storage requirements</u>	<u>Acceptable</u>
<i>Recommended labeling practices: USP General Chapters <7> Labeling USP General Chapters <659> Packaging and Storage Requirements</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Dispensing container</u>	<u>Acceptable</u>
21 CFR 201.100	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>USP monograph for Bacteriostatic Water for Injection, USP vial</u> <i>Packaging and Storage: Preserve in single-dose or multiple-dose glass or plastic containers. Glass containers are preferably of Type I or Type II glass, of not larger than 30-mL size.</i> <i>Labeling: Label it to indicate the name(s) and proportion(s) of the added antimicrobial agent(s). Label it also to include the statement "Not For Use In Newborns", in boldface capital letters on the label immediately under the official name, printed in a contrasting color, preferably red. Alternatively, the statement may be placed prominently elsewhere on the label if the statement is enclosed within a box.</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Comment/Recommendation:</u> Pfizer provided the following comment regarding the omitted "USP" in the product name: <i>based on an email exchange and agreement between the Applicant and FDA Project Manager dated 5 February 2018, Pfizer has purposefully omitted "USP" in the carton labeling. The rationale for this is while the 1.1% benzyl alcohol BWFI solution accompanying Trazimera 420 mg/vial complies with the USP Monograph: Bacteriostatic Water for Injection in all other aspects, Pfizer is proposing a pH range of 4.5-8.0, as opposed to the pH range of 4.5-7.0 described in the USP monograph. As such Pfizer did not claim USP-compliance.</i> <i>We find the applicant's response acceptable.</i>	

Package⁵ Label Evaluation

<u>Proper name</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Manufacturer name, address, and license number</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Recommended labeling practices: OBP Recommended practice (OPQ-OBP-RP-014)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Lot number or other lot identification</u>	<u>Acceptable</u>
21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Expiration date</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.17	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Preservative</u>	<u>Acceptable</u>
21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Comment/Recommendation: Ensure "No preservative" appears on the carton labeling (See 21 CFR 610.61 (e)). "No preservative" may appear on the side panel prior to the "No US standard of potency" statement. <i>The applicant revised as requested</i>	
<u>Number of containers</u>	<u>Acceptable</u>
21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Strength/volume</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.10, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176</i> <i>USP General Chapters: <7> Labeling</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Storage temperature/requirements</u>	<u>Acceptable</u>

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.

21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Recommended labeling practices: USP General Chapters: <7> Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Handling: "Do Not Shake", "Do not Freeze" or equivalent</u>	<u>Acceptable</u>
21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Multiple dose containers (recommended individual dose)</u>	<u>Acceptable</u>
21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Route of administration</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.5, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices: route of administration statement recommended locations</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Known sensitizing substances</u>	<u>Acceptable</u>
21 CFR 610.61	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Inactive ingredients</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices: USP General Chapters <1091> Labeling of Inactive Ingredients USP General Chapters <7> Labeling</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Source of the product</u>	<u>Acceptable</u>
21 CFR 610.61	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Minimum potency of product</u>	<u>Acceptable</u>
21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Rx only</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

Recommended labeling practices: prominence of Rx Only	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Divided manufacturing</u>	<u>Acceptable</u>
21 CFR 610.63 (Divided manufacturing responsibility to be shown)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Distributor</u>	<u>Acceptable</u>
21 CFR 610.64 (Name and address of distributor)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Bar code</u>	<u>Acceptable</u>
21 CFR 610.67, 21 CFR 201.25	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Recommended labeling practices: <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>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u>	<u>Acceptable</u>
21 CFR 610.68, 21 CFR 201.26	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>NDC numbers</u>	<u>Acceptable</u>
21 CFR 201.2, 21 CFR 207.35	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Preparation instructions</u>	<u>Acceptable</u>
21 CFR 201.5	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430) USP General Chapters <7> Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Package type term</u>	<u>Acceptable</u>
<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. USP chapter <659> Packaging and Storage Requirements</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Misleading statements</u>	<u>Acceptable</u>
21 CFR 201.6	<input checked="" type="checkbox"/> Yes

	<input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Prominence of required label statements</u>	<u>Acceptable</u>
21 CFR 201.15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Spanish-language (Drugs)</u>	<u>Acceptable</u>
21 CFR 201.16	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u>	<u>Acceptable</u>
21 CFR 201.20	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Phenylalanine as a component of aspartame</u>	<u>Acceptable</u>
21 CFR 201.21	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Sulfites; required warning statements</u>	<u>Acceptable</u>
21 CFR 201.22	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Net quantity</u>	<u>Acceptable</u>
21 CFR 201.51	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Recommended labeling practices: <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Usual dosage statement</u>	<u>Acceptable</u>
21 CFR 201.55, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Dispensing container</u>	<u>Acceptable</u>
21 CFR 201.100	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Medication Guide</u>	<u>Acceptable</u>
21 CFR 610.60, 21 CFR 208.24	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

Prescribing Information and Patient Labeling Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
21 CFR 201.57(a)(2)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices: Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices: USP nomenclature for diluents and intravenous solutions</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
DOSAGE FORMS AND STRENGTHS	Acceptable
21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176</i> <i>USP General Chapters: <7> Labeling</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
21 CFR 201.57(c)(3)(iv)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices: USP nomenclature for diluents and intravenous solutions</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p>Comment/Recommendation: The applicant deleted the statement (b) (4) but retained the description of "lyophilized (b) (4) in this section of the labeling. Confirm if your lyophilized powder has a cake-like appearance.</p> <p><i>The applicant confirmed that the lyophilized powder has a cake-like appearance and added the statement accordingly. However, the applicant asked to confirm acceptance of the deletion of the statement (b) (4) We agree to delete provided that the (b) (4) does not</i></p>	

apply to your product. We left the statement in to verify that this is your intent to remove this instruction with the clarification of the appearance of your lyophilized powder.

The applicant removed the (b) (4) OBP labeling determined this is acceptable since the applicant determined that this statement does not apply to their product

3 DOSAGE FORMS AND STRENGTHS	Acceptable
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21 CFR 201.57(c)(4)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
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Comment/Recommendation: We deleted "preservative-free" since it is not considered an identifying characteristic of the dosage form and this information is provided in section 11 (Description).

The applicant revised as requested

<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)</i> <i>USP General Chapters <659>, USP General Chapters <7></i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
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11 DESCRIPTION	Acceptable
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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)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
---	--

<i>Recommended labeling practices:</i> <i>USP General Chapters <1091>, USP General Chapters <7></i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
--	--

Comment/Recommendation:

We deleted the proprietary name since this paragraph discusses the drug substance.

The applicant revised as requested

We relocated the dosage from "for injection" to appear after the proper name.

The applicant revised as requested

Confirm if your lyophilized product has a cake-like appearance.

The applicant confirmed that the lyophilized powder has a cake-like appearance and added the statement accordingly.

16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
--	-------------------

21 CFR 201.57(c)(17)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
----------------------	--

<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
--	--

Comment/Recommendation:

We relocated the word "sterile" to appear in front of the word "white" instead of "powder"

We deleted the word (b) (4) since this section of the labeling describes the storage conditions for the supplied product which is not yet opened and the storage requirements for

reconstituted product are described in section 2 and not here in section 16 thus it does not warrant the distinction here.

The applicant revised as requested

We revised the last paragraph describing the alternative room temperature for readability follows: "If needed, unopened TRAZIMERA vials may be removed from the refrigerator and stored at room temperature up to 30°C (86°F) for a single period of up to 3 months. Once removed from the refrigerator, do not return to the refrigerator and discard after 3 months or by the expiration date stamped on the vial, whichever occurs first. Write the revised expiration date in the space provided on the carton labeling"

The applicant revised as requested

MANUFACTURER INFORMATION	Acceptable
21 CFR 201.100(e), 21 CFR 201.1, 19 CFR 134.11	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Recommended labeling practices: <i>21 CFR 610.61 (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>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on February 5, 2019)

<\\cdsesub1\evsprod\bla761081\0058\m1\us\lab-0995-xx-pkg-insert-clean.pdf>)

Container Labels (submitted on January 29, 2019)

(b) (4)



Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 2/05/2019 03:55:29PM
GUID: 50814c7000007a3d59329f660d8ddf02



Lymarie
Maldonado-Baez

Digitally signed by Lymarie Maldonado-Baez
Date: 2/05/2019 03:56:44PM
GUID: 5ac7de300070e5e69fb599e6b33f405e

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 1, 2019
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761081
Product Name and Strength:	Trazimera ^a (trastuzumab-qyyp) ^b for Injection, 420 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Ireland Pharmaceuticals (Pfizer)
FDA Received Date:	February 20, 2018, October 30, 2018, and January 29, 2019
OSE RCM #:	2017-1260-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

^a The proposed proprietary name (Trazimera) is only conditionally accepted for this product until the application is approved; see Gao, T. Proprietary Name Review for Trazimera (BLA 761081). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Nov 26. OSE RCM No.: 2018-26469926.

^b The proposed nonproprietary name (trastuzumab-qyyp) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Nonproprietary Name Suffix for Trazimera (BLA 761081). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 28. OSE RCM No.: 2017-1261-1.

1 REASON FOR REVIEW

As part of the 351(k) BLA 761081 review for Trazimera (trastuzumab-qyyp) for Injection, this review evaluates the proposed Trazimera prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Pfizer previously submitted the 351(k) BLA 761081 on June 22, 2017.

Labels and Labeling

We previously completed a label and labeling review for this BLA 761081, and found the container label and carton labeling received on February 20, 2018 acceptable from a medication error perspective.^c

Nonproprietary Name

On June 22, 2017, Pfizer also submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of their product.^d

On February 28, 2018^e, we found the nonproprietary name, trastuzumab-qyyp, conditionally acceptable for BLA 761081.

On April 6, 2018, our recommendations to revise the proposed labels and labeling accordingly were communicated to Pfizer in a General Advice letter.^f

However, BLA 761081 received a Complete Response letter on April 20, 2018 due to issues with product quality.^g

Therefore, Pfizer submitted a complete response to the Agency's complete response letter on September 28, 2018. On January 7, 2019, we notified the applicant that the nonproprietary name, trastuzumab-qyyp, remained conditionally acceptable for BLA 761081 and our recommendations to revise the proposed labels and labeling accordingly were communicated to Pfizer in a General Advice letter.^h

^c Gao, T. Label and Labeling Review for Trazimera (BLA 761081). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 9. RCM No.: 2017-1260.

^d BLA 761081. Request for Review of Nonproprietary Naming. New York (NY): Pfizer Inc.; 2017 JUNE 22. Available from: <\\cdsesub1\evsprod\bla761081\0001\m1\us\request-review-nonproprietary-naming.pdf>.

^e Gao, T. Nonproprietary Name Suffix for Trazimera (BLA 761081). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Feb 28. OSE RCM No.: 2017-1261.

^f Harris, D. General Advice Letter for BLA 761081. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 2018 APR 6.

^g Amiri-Kordestani, L. Complete Response for BLA 761081. Silver Spring (MD): FDA, CDER, OND, DOP1 (US); 2018 APR 20. BLA 761081.

^h Harris, D. General Advice Letter for BLA 761081. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 2019 JAN 7.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 PRESCRIBING INFORMATION (PI)

The PI received on October 30, 2018 is not acceptable from a medication error perspective because the nonproprietary name lacks the suffix, -qyyp, appended to the core name, trastuzumab.

In the Dosage and Administration section, there is a slash mark "/" in "docetaxel/carboplatin", which could be misinterpreted to mean "docetaxel or carboplatin" instead of "docetaxel and carboplatin". The slash mark "/" in "docetaxel/carboplatin" should be revised to "docetaxel and carboplatin" for clarity and to minimize the risk of confusion.

3.2 CONTAINER LABEL AND CARTON LABELING

We reviewed the February 20, 2018 Trazimera container label and carton labeling and determined that they may be improved to promote safe use of the product. We provided the following recommendations to Office of Pharmaceutical Quality (OPQ) Labeling Reviewer to get OPQ concurrence. DOP1 communicated our recommendations below in addition to OPQ's labeling comments to Pfizer on January 22, 2019.¹

¹ Lee, C. FDA Communication: BLA 761081/Information Request. Silver Spring (MD): FDA, CDER, OND, OHOP, DOP1 (US); 2019 January 22. BLA 761081.

A. General Comments (Container labels & Carton Labeling)

1. Revise the nonproprietary name on all labels and labeling to incorporate the FDA-designated nonproprietary name suffix, -qyyp, appended to the core name, trastuzumab so that the proper name appears as trastuzumab-qyyp throughout the labels and labeling. This recommendation was communicated to you in the January 7, 2019 General Advice Letter.
2. Consider revising the expiration date to the format YYYY-MMM. We note you previously agreed to use the format MMMYYYY (e.g., JAN2018) to define the expiration date in response to January 31, 2018 FDA Information Request.^j However, since that time, FDA's current thinking has been published in the new *Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers*. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

Pfizer submitted revised Trazimera container labels and carton labeling on January 29, 2019 in response to our recommendations above and OPQ's labeling comments. Pfizer agrees to the recommendation to reformat the expiration date to reflect FDA's current thinking and utilize the YYYY-MM-DD format. Pfizer further explained that the expiration dating is printed during packaging at the site, and does not appear on the current submitted artwork but will be reflected as YYYY-MM-DD.^k

The revised Trazimera container labels and carton labeling received on January 29, 2019 are acceptable from a medication error perspective.

^j BLA 761081 Trazimera (trastuzumab-xxxx) Response to 31 January 2018 FDA Information Request. Ringaskiddy (Cork, Ireland): Pfizer Ireland Pharmaceuticals. 2018 FEB 20. Available from <\\cdsesub1\evsprod\bla761081\0032\m1\us\response-ir-31jan18.pdf>.

^k Response to Information Request (Container and Carton Labeling) for BLA 761081 for PF-05280014, a Proposed Biosimilar to Herceptin. Ringaskiddy (Cork, Ireland): Pfizer Ireland Pharmaceuticals. 2019 Jan 29. Available from <\\cdsesub1\evsprod\bla761081\0055\m1\us\cover.pdf>.

4 CONCLUSION & RECOMMENDATIONS

The January 29, 2019 revised Trazimera container labels and carton labeling are acceptable from a medication error perspective. The proposed Trazimera PI may be improved to ensure safe medication use. We provide specific recommendations in Sections 4.1 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Prescribing Information

- a. Revise the nonproprietary name on all labels and labeling to incorporate the suffix, -qyyp, appended to the core name, trastuzumab so that the nonproprietary name appears as trastuzumab-qyyp throughout the labels and labeling.

We note this was communicated to the Applicant in the January 7, 2019 General Advice letter.

b. Dosage and Administration Section

- i. There is a slash mark "/" in "docetaxel/carboplatin", which could be misinterpreted to mean "docetaxel or carboplatin" instead of "docetaxel and carboplatin". Revise the slash mark "/" in "docetaxel/carboplatin" to "docetaxel and carboplatin" for clarity and to minimize the risk of confusion.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Trazimera received on October 30, 2018 from Pfizer Ireland Pharmaceuticals, and Herceptin retrieved from November 29, 2018 approved Herceptin Prescribing Information.

Table 2. Relevant Product Information for Herceptin and Trazimera		
Product Name	Herceptin ¹	Trazimera
Initial Approval Date	N/A	N/A
Active Ingredient	Trastuzumab	trastuzumab-qyyp
Indication	Adjuvant breast cancer Metastatic breast cancer Metastatic gastric cancer	Adjuvant breast cancer Metastatic breast cancer Metastatic gastric cancer
Route of Administration	Intravenous	Intravenous
Dosage Form	for Injection	for Injection
Strength	420 mg/vial, 150 mg/vial	420 mg/vial
Dose and Frequency	<p>Adjuvant Treatment of HER2-Overexpressing Breast Cancer</p> <p>Administer at either:</p> <ul style="list-style-type: none"> Initial dose of 4 mg/kg over 90 minute intravenous infusion, then 2 mg/kg over 30 minute intravenous infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel and carboplatin). One week after the last weekly dose of [trastuzumab], administer 6 mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks to complete a total of 52 weeks of therapy, or Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30 to 90 minutes IV infusion every three weeks for 52 weeks. <p>Metastatic HER2-Overexpressing Breast Cancer</p> <ul style="list-style-type: none"> Initial dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute intravenous infusions. <p>Metastatic HER2-Overexpressing Gastric Cancer</p> <ul style="list-style-type: none"> Initial dose of 8 mg/kg over 90 minutes intravenous infusion, followed by 6 mg/kg over 30 to 90 minutes intravenous infusion every 3 weeks. 	

¹ Herceptin [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 Nov 19. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103792s53451bl.pdf.

Table 2. Relevant Product Information for Herceptin and Trazimera		
Product Name	Herceptin ¹	Trazimera
How Supplied	<p>420 mg/vial: Herceptin (trastuzumab) for injection 420 mg/vial is supplied in a multiple-dose vial as a lyophilized sterile powder, under vacuum. Each carton contains one multiple-dose vial of Herceptin and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.</p> <p>150 mg/vial: Herceptin (trastuzumab) for injection 150 mg/vial is supplied in a single-dose vial as a lyophilized sterile powder, under vacuum. Each carton contains one single-dose vial of Herceptin.</p>	<p>420 mg/vial: (b) (4)</p> <p>(b) (4) Each carton contains one multiple-dose vial of TRAZIMERA and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI) containing 1.1% benzyl alcohol as a preservative.</p>
Storage	Store Herceptin vials in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.	Store (b) (4) TRAZIMERA vials in the refrigerator at 2°C to 8°C (36°F to 46°F) (b) (4)
Container Closure	<p>Single dose vial - 15 mL (b) (4) vial with 20 mm (b) (4) stopper and aluminum seal with flip-off cap.</p> <p>Multi dose vial - 50 mL (b) (4) vial with 20 mm (b) (4) stopper and aluminum seal with flip-off cap.</p>	<p>30 mL (b) (4) clear glass vial with (b) (4) stopper and crimp seal with flip-off cap.</p>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 17, 2018, we searched for previous DMEPA reviews relevant to this current review using the term, Trazimera. Our search retrieved 1 previous review^m, and we confirmed that our previous recommendations were implemented.

We also searched for previous DMEPA reviews relevant to this current review using the term, trastuzumab, since the date of our last searchⁿ. Our search identified 1 previous review^o, and we considered our previous recommendations to see if they are applicable for this current review.

^m Gao, T. Label and Labeling Review for Trazimera (BLA 761081. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 9. RCM No.: 2017-1260.

ⁿ Date of our last search on August 9, 2018 in Gao, T. Label and Labeling Review for Herzuma (BLA 761091. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 22. RCM No.: 2018-1291.

^o Gao, T. Label and Labeling Review for Herzuma (BLA 761091. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 22. RCM No.: 2018-1291.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 17, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter since our last search on August 9, 2018^p. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR
Search Strategy and Terms	Match Exact Word or Phrase: trastuzumab

D.2 Results

The search retrieved no relevant articles associated with label and labeling for trastuzumab.

^p August 9, 2018, date of our last ISMP Newsletters search in Gao, T. Label and Labeling Review for Herzuma (BLA 761091. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 22. RCM No.: 2018-1291.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^q along with postmarket medication error data, we reviewed the following Trazimera labels and labeling submitted by Pfizer Ireland Pharmaceuticals.

- Container label received on February 20, 2018
- Revised container labels received on January 29, 2019
- Diluent label received on February 20, 2018
- Carton labeling received on February 20, 2018
- Revised carton labeling received on January 29, 2019
- Prescribing Information (Image not shown) received on October 30, 2018

G.2 Label and Labeling Images

Container label – Trazimera vial – received on February 20, 2018

(b) (4)



^q Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

TINGTING N GAO
02/01/2019 01:03:12 PM

CHI-MING TU
02/01/2019 01:33:28 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 25, 2019

To: Julia Beaver, M.D., Director
Division of Oncology Products (DOP1)

Clara Lee, PharmD, Regulatory Project Manager, DOP1

William Pierce, PharmD, Associate Director for Labeling, DOP1

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, PharmD, M.B.A., Team Leader, OPDP

Subject: OPDP Labeling Comments for Trazimera[™] (trastuzumab-qyyp)¹ for injection, for intravenous use

BLA: 761081

In response to DOP1's consult request dated October 25, 2018, OPDP has reviewed the proposed product labeling (PI), container label and carton labeling for the BLA submission, Trazimera[™] (trastuzumab-qyyp) for injection, for intravenous use (Trazimera).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1 (Clara Lee) on January 17, 2019, and we do not have any comments.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 20, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

^{1 1} The proposed proprietary name (Trazimera) and the proper name with suffix (trastuzumab-qyyp) are conditionally accepted until such time that the application is approved.

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/

KEVIN WRIGHT
01/25/2019 10:49:55 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 9, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761081
Product Name and Strength:	Trazimera (trastuzumab-qyyp) ^a for Injection, 420 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfizer, Inc.
FDA Received Date:	January 8, 2018 and February 20, 2018
OSE RCM #:	2017-1260
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

^a Trazimera has been developed as a proposed biosimilar to US-licensed Herceptin (Trastuzumab). Both the proprietary name (Trazimera) and proper name (trastuzumab-qyyp) have been conditionally accepted.

1 REASON FOR REVIEW

As part of the 351(k) BLA 761081 review for Trazimera (trastuzumab-qyyp) for Injection^b, this review responds to a DOP1 consult requesting DMEPA to review the proposed Trazimera prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 PRESCRIBING INFORMATION (PI)

We reviewed the proposed Trazimera PI and find it acceptable from a medication error perspective.

3.2 CONTAINER LABEL AND CARTON LABELING

We reviewed the January 8, 2018 proposed Trazimera container labels and carton labeling and determined that they be may be improved to promote safe use of the proposed product. We provide the following recommendations to Office of Pharmaceutical Quality (OPQ) Labeling

^b a proposed biosimilar to Herceptin (trastuzumab) for Injection, BLA 103792

Reviewer to get OPQ concurrence. DOP1 communicated our recommendations below in addition to OPQ's labeling comments to Pfizer on January 31, 2018.^c

A. General comments

1. Consider removing the (b) (4) since it is located near the expiration date and may be confused as the expiration date.
2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format such as MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).^d

B. Container label and Carton Labeling

1. Revise the strength statement to "420 mg/vial" or "420 mg per vial" per Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.^d
2. Relocate the route of administration statement from the side panel to appear on the principal display panel (PDP) and revise this statement to read "For intravenous infusion after reconstitution".

C. Diluent label

1. As currently presented, the net quantity statement "20 mL VIAL" is more prominent than the product name Bacteriostatic Water for Injection. We recommend increase the font size of the product name and relocate the net quantity statement "20 mL VIAL" away from the product name to increase prominence of the product name.

Pfizer submitted revised Trazimera container labels and carton labeling on February 20, 2018 in response to our recommendations above and OPQ's labeling comments. Also, Pfizer agreed to present the expiration date as MMMYYYY.^e The revised Trazimera container labels and carton labeling are acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Trazimera Prescribing Information and the February 20, 2018 revised Trazimera container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

^c The following recommendations were communicated to Pfizer on January 31, 2018 in Lee, C. Information Request for "FDA Communication: BLA 761081/Information Request-Container-Carton" Message to Scott Anderson. Silver Spring (MD): FDA, CDER, OND, DOP1 (US); 2018 JAN 31.

^d Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^e Pfizer. BLA 761081 Trazimera (trastuzumab-xxxx) Response to 31 January 2018 FDA Information Request. Ringaskiddy (Cork, Ireland): Pfizer Ireland Pharmaceuticals. 2018 FEB 20. Available from <\\cdsesub1\evsprod\bla761081\0032\m1\us\response-ir-31jan18.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Trazimera that Pfizer submitted on January 8, 2018, and Herceptin retrieved from April 27, 2017 approved Herceptin Prescribing Information^f.

Table 2. Relevant Product Information for Herceptin and Trazimera		
Product Name	Herceptin	Trazimera
Initial Approval Date	September 25, 1998	N/A
Active Ingredient	trastuzumab	trastuzumab-qyyp
Indication	HER2 overexpressing breast cancer HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	
Route of Administration	Intravenous	Intravenous
Dosage Form	For injection	For injection
Strength	150 mg/vial, 420 mg/vial	420 mg/vial
Dose and Frequency	Adjuvant Treatment of HER2 Overexpressing Breast Cancer Administer at either: <ul style="list-style-type: none">Initial dose of 4 mg/kg over 90 minute intravenous infusion, then 2 mg/kg over 30 minute intravenous infusion weekly for the first 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy.Initial dose of 8 mg/kg over 90 minutes intravenous infusion, then 6 mg/kg over 30-90 minutes intravenous infusion every three weeks for 52 weeks. Metastatic HER2 Overexpressing Breast Cancer <ul style="list-style-type: none">Initial dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute intravenous infusions. Metastatic HER2 Overexpressing Gastric Cancer <ul style="list-style-type: none">Initial dose of 8 mg/kg over 90 minutes intravenous infusion, followed by 6 mg/kg over 30 to 90 minutes intravenous infusion every 3 weeks.	

^f Herceptin. Drugs@FDA. U.S. Food and Drug Administration; April 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103792s5337lbl.pdf.

Table 2. Relevant Product Information for Herceptin and Trazimera		
Product Name	Herceptin	Trazimera
How Supplied	One carton containing 150 mg Single dose vial One carton containing 420 mg multi-dose vial and Bacteriostatic Water for Injection	One carton containing 420 mg multi-dose vial and Bacteriostatic Water for Injection
Storage	Store in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.	
Container Closure	Single dose vial - 15 mL (b) (4) vial with 20 mm (b) (4) stopper and aluminum seal with flip-off cap Multi dose vial - 50 mL (b) (4) vial with 20 mm (b) (4) stopper and aluminum seal with flip-off cap	30 mL (b) (4) clear glass vials with (b) (4) stoppers and (b) (4) with flip-off caps

APPENDIX B. PREVIOUS DMEPA REVIEWS

Although this is the first label and labeling review we conducted for BLA 761081, we searched DMEPA's previous reviews using the terms, trastuzumab, to review our previous recommendations for Herceptin and 351(k) trastuzumab products to ensure our recommendations for Pfizer's proposed Trazimera (trastuzumab-qyyp) for Injection product are consistent with our previous recommendations for other trastuzumab products. This search was conducted on February 1, 2018.

Trastuzumab products				
Application	Applicant	Strength	Status	OSE Review
BLA 103792 Herceptin (trastuzumab) for Injection	Genentech	150 mg/vial 420 mg/vial	Approved	2013-2816 ^g
			420 mg/vial (originally	2014-1298 ^h
			labeled as 440 mg/vial):	2016-2396 ⁱ
			September 25, 1998	2016-2396-1 ^j
			150 mg/vial: April 27, 2017	2017-463 ^k 2017-463-1 ^l
BLA 761074 Ogivri (trastuzumab-dkst) for Injection	Mylan	420 mg/vial	Approved December 1, 2017	2016-2560 ^m
BLA 761081 Trazimera (trastuzumab-qyyp) for Injection	Pfizer	420 mg/vial	Subject of this review	2017-1260

^g Abdus-Samad, J. Label and Labeling Review for Herceptin (BLA 103792/S-5311). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 28. RCM No.: 2013-2816.

^h Davis, M. DMEPA Postmarket Signal Write Up for Herceptin (Trastuzumab) BLA 103792. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 16. RCM No.: 2014-1298.

ⁱ Gao, T. Label and Labeling Review for Herceptin (Trastuzumab) BLA 103792/S-5336. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Nov 1. RCM No.: 2016-2396.

^j Gao, T. Memorandum Review of Revised Label and Labeling for Herceptin (Trastuzumab) BLA 103792/S-5336. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Feb 10. RCM No.: 2016-2396-1.

^k Gao, T. Label and Labeling and Postmarketing Communication Plan Review for Herceptin (NDA BLA 103792/5339). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 15. OSE RCM No.: 2017-463.

^l Gao, T. Memorandum Review of Revised Label and Labeling for Herceptin (Trastuzumab) BLA 103792/5339. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Feb 10. RCM No.: 2017-463-1.

^m Gao, T. Label and Labeling Review for Ogivri (trastuzumab-dkst) for Injection (BLA 761074). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 4. RCM No.: 2016-2560.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 13, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care and Community
Search Strategy and Terms	Match Exact Word or Phrase: trastuzumab

D.2 Results

The search did not retrieve relevant results.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,ⁿ along with postmarket medication error data, we reviewed the following Trazimera labels and labeling submitted by Pfizer.

- Container labels received on January 8, 2018
- Revised container labels received on February 20, 2018
- Carton labeling received on January 8, 2018
- Revised carton labeling received on February 20, 2018
- Prescribing Information (Image not shown) submitted January 8, 2018

ⁿ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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03/09/2018

CHI-MING TU
03/12/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 5, 2018

To: Julia Beaver, M.D., Acting Director
Division of Oncology Products (DOP1)

Clara Lee, PharmD, Regulatory Project Manager, (DOP1)

William Pierce, PharmD, Associate Director for Labeling, (DOP1)

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, PharmD, M.B.A., Team Leader, OPDP

Subject: OPDP Labeling Comments for Trazimera[™] (trastuzumab-xxxx) for injection, for intravenous use

BLA: 761081

In response to DOP1's consult request dated August 10, 2017, OPDP has reviewed the proposed product labeling (PI), container label and carton labeling for the BLA submission, Trazimera[™] (trastuzumab-xxxx) for injection, for intravenous use (Trazimera).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1 (Clara Lee) on February 20, 2018, and we do not have any comments.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 20, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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

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/s/

KEVIN WRIGHT
03/05/2018