CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761091Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	December 14, 2018
From	Sanjeeve Balasubramaniam, MD, MPH (CDTL) Laleh Amiri-Kordestani, MD (Supervisory Associate Director, DOP1)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 761091
Applicant	Celltrion, Inc.
Date of Submission	May 30, 2017; resubmitted June 15, 2018
BSUFA Goal Date	December 15, 2018
Proprietary Name	CT-P6 (also referred to as Herzuma by the Applicant)[1]
Nonproprietary Name	trastuzumab-pkrb[1]
Dosage Form(s) and Strengths	For Injection: 420 mg lyophilized powder in a multiple-dose vial for reconstitution
Applicant Proposed Indication(s)/Population(s)	HERZUMA is a HER2/neu receptor antagonist indicated for: • the treatment of HER2 overexpressing breast cancer.
Applicant Proposed Dosing Regimen(s)	Adjuvant Treatment of HER2-Overexpressing Breast Cancer • Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel and carboplatin). One week after the last weekly dose of HERZUMA, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy. Metastatic HER2-Overexpressing Breast Cancer • Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	HERZUMA is a HER2/neu receptor antagonist indicated for: • the treatment of HER2 overexpressing breast cancer.
Recommended Dosing Regimen(s) (if applicable)	Adjuvant Treatment of HER2-Overexpressing Breast Cancer • Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel and carboplatin). One week after the last weekly dose of HERZUMA, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy. Metastatic HER2-Overexpressing Breast Cancer • Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

[1] For purposes of this review, the proposed product is referred to by the applicant's descriptor CT-P6, which was the name used to refer to this product during development. The proposed proprietary name (Herzuma) and proposed nonproprietary name (trastuzumab-pkrb) are only conditionally accepted until the application is approved.

1. Background

On May 30, 2017, the applicant submitted biologics license application (BLA) 761091 under Section 351(k) of the Public Health Service Act for CT-P6, a proposed biosimilar to US-licensed Herceptin (trastuzumab; henceforth referred to as US-Herceptin)[2]. At that time, the applicant was seeking licensure of CT-P6 for the same indications as US-Herceptin, namely for adjuvant treatment of breast cancer, metastatic breast cancer, and metastatic gastric cancer. During the review of the initial submission for CT-P6, the Agency concluded that the applicant had adequately demonstrated biosimilarity, but issued a complete response (CR) letter to the applicant on the basis of facility and product quality deficiencies.

Section 351(i) of the Public Health Service Act (PHS Act) defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the proposed biosimilar and the reference product in terms of the safety, purity, and potency of the product." Both parts of the statutory definition must be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a determination that the products are highly similar.

The applicant conducted an analytical comparison between the proposed biosimilar and US-Herceptin to support the demonstration that CT-P6 is highly similar to US-Herceptin. The applicant also conducted a head-to-head comparison of the non-clinical PK and toxicity profiles of CT-P6 and US-Herceptin via intravenous administration in cynomolgus monkeys. Further, the applicant conducted a clinical PK similarity study, CT-P6 1.5, and a comparative clinical study, CT-P6 3.2 (henceforth referred to as study 3.2), to support the demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin.

The analytical data supported the determination that CT-P6 is highly similar to US-Herceptin notwithstanding minor differences in clinically inactive components. In addition, the data submitted from the clinical development program of CT-P6 supported a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. Together, the totality of the data thus supported the demonstration of biosimilarity of CT-P6 to US-Herceptin during the initial review of the dossier. The applicant also provided adequate scientific justification for extrapolation of data to support licensure of CT-P6 under Section 351(k) as a biosimilar for the conditions of use for which US-Herceptin has been previously approved and for which the applicant sought licensure.

[2] In this document, any reference to "Herceptin" should be considered a reference to US-licensed Herceptin. References to unknown sources of trastuzumab (e.g., based on historical studies) will use "trastuzumab".

However, the manufacturing and control data submitted in the original application were not sufficient to support a conclusion that the manufacture of CT-P6 was well controlled and would lead to a product that is pure and potent for the duration of the shelf life; additional facility deficiencies were also documented. A CR letter for facility and product quality deficiencies (related to manufacturing and control data) was issued on March 30, 2018.

On June 15, 2018, the applicant submitted responses to address deficiencies identified in the CR letter in their BLA (761091) Class 2 Resubmission. The applicant has modified the requested indications for their product. The requested indications now are:

Adjuvant breast cancer:

CT-P6 is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer)

- As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- As part of a treatment regimen with docetaxel and carboplatin

Metastatic breast cancer (MBC):

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

2. Product Quality

Discipline	Reviewer	Branch/Division
Drug Substance	Riley Myers	OPQ/OBP/DBRR I
Drug Product	Shadia Zaman	OPQ/OBP/DBRR I
Drug Substance Microbiology Drug Product Microbiology	Scott Nichols Candace Gomez-Broughton	OPQ/OPF/DMA IV OPQ/OPF/DMA IV
Facility	Thuy Thanh Nguyen	OPQ/OPF/DIA
Immunogenicity assay	Shadia Zaman	OPQ/OBP/DBRR I
Analytical Similarity	Riley Myers	OPQ/OBP/DBRR I
Labeling	Vicky Borders Hemphill	OPQ/OBP
Product Quality Team Lead Microbiology QAL Facility Branch Chief	Jennifer Swisher Reyes Candau-Chacon Peter Qiu	OPQ/OBP/DBRR I OPQ/OPF/DMA IV OPQ/OPF/DIA
CMC RPBM	Andrew Shiber	OPQ/OPRO
Application Team Lead	Jennifer Swisher	OPQ/OBP/DBRR I

The product quality deficiencies (related to manufacturing and controls) described in the CR letter dated February 28, 2018 have been addressed in the resubmission. Overall, the OPQ

review of manufacturing and controls in the resubmission and in the initial BLA submission have confirmed that the processes and methods used for drug substance and drug product manufacturing, release, and stability testing are sufficient to assure a consistent and safe product.

The commercial manufacture of CT-P6 drug substance (DS) and drug product (DP) at Celltrion, Inc. (Incheon, Republic of Korea) is recommended for approval by the Division of Inspectional Assessment (DIA, OPF, OPQ), as a prelicense inspection performed during the resubmission review cycle (August 20-28, 2018) was classified as Voluntary Action Indicated (VAI). A prelicense inspection was not conducted during the first review cycle due to the Official Action Indicated (OAI) status of the facility associated with a Warning Letter (WL 320-18-28) issued to the firm based on a post-approval inspection for BLA 125544 (Inflectra) and a GMP surveillance inspection.

Key changes made by the applicant during this review cycle are included in the CMC executive summary dated November 19, 2018.

An inspection of Celltrion was conducted by FDA from August 20-28, 2018. This inspection covered CT-P6 DS and DP manufacture as well as the QC laboratories and the similarity assessment data. There were no issues with the similarity data, but a seven-item FDA Form-483 was issued upon completion of the inspection. The DIA review team deemed the sponsor's responses to the Form-483 items adequate and recommended approval of the facility for BLA 761091. The compliance status of the DS and DP manufacturing facility is acceptable.

3. Nonclinical Pharmacology/Toxicology

Refer to the CDTL review filed in DARRTS on March 29, 2018.

4. Clinical Pharmacology

Refer to the CDTL review filed in DARRTS on March 29, 2018.

5. Clinical Microbiology

Refer to the CDTL review filed in DARRTS on March 29, 2018.

6. Clinical/Statistical- Efficacy

Refer to the CDTL review filed in DARRTS on March 29, 2018.

7. Safety

Refer to the CDTL review filed in DARRTS on March 29, 2018.

8. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

9. Pediatrics

Refer to the CDTL review filed in DARRTS on March 29, 2018.

10. Other Relevant Regulatory Issues

Refer to the CDTL review filed in DARRTS on March 29, 2018.

11. Labeling

Prescribing Information

The draft labeling submitted by the applicant to BLA 761091 on December 13, 2018 is adequate from a review perspective.

12. Recommendations

Recommended Regulatory Action
All deficiencies included in the March 30, 2018 CR letter have been adequately addressed by the applicant. In considering the totality of the evidence, the data submitted by the applicant show that CT-P6 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between CT-P6 and US-Herceptin in terms of safety, purity and potency; therefore, we recommend approval of BLA 761091 for CT-P6 as a biosimilar to US-Herceptin for the following indications for which US-Herceptin is currently licensed and for which Celltrion is seeking licensure:

Adjuvant breast cancer:
CT-P6 is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer)

- As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- As part of a treatment regimen with docetaxel and carboplatin

Metastatic breast cancer (MBC):

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Risk Evaluation and Management Strategies (REMS)

A REMS is not indicated.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Office of Clinical Pharmacology Post-Marketing Commitment:

Submit additional long-term storage stability data on CT-P6 for 559 days covering the duration of the study from the date of sample collection to the last sample analysis date.
Final Report Submission: March, 2019

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/

SANJEEVE BALASUBRAMANIAM
12/14/2018

LALEH AMIRI KORDESTANI
12/14/2018

Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
From	Sanjeeve Balasubramaniam, M.D., M.P.H. (CDTL) Julia Beaver, M.D. (Division Director)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	351(k) BLA 761091
Applicant	Celltrion
Date of Submission	5/30/2017
BsUFA Goal Date	3/30/2018
Proprietary Name / Established (USAN) names	HERZUMA/Trastuzumab-(b) (4) CT-P6[1] Lyophilized Powder for Intravenous Infusion
Dosage forms / Strength	lyophilized powder for injection/420 mg per vial
Proposed Indication(s)	HERZUMA is a HER2/neu receptor antagonist indicated for: 1. Adjuvant breast cancer: a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel b. With docetaxel and carboplatin c. As a single agent following multi-modality anthracycline based therapy 2. Metastatic breast cancer (MBC): a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease 3. Metastatic gastric cancer: a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease
Recommended:	*Complete Response*
Recommended Indication (if applicable)	Not applicable

[1] For purposes of this review, the proposed product is referred to by the Sponsor's descriptor CT-P6, which was the name used to refer to this product during development. The proprietary name (Herzuma) and proper name (trastuzumab-(b) (4)) for this proposed product have been conditionally accepted.

APPEARS THIS WAY ON ORIGINAL

REVIEW TEAM

Product Quality (CMC) Review Team:

Drug Substance and Analytical Similarity: Riley Myers
Drug Product and Immunogenicity Assay: Shadia Zaman and Rachel Novak (TL)
Drug Substance Microbiology: Scott Nichols
Drug Product Microbiology: Candace Gomez-Broughton
Facility: Thuy Thanh Nguyen and Peter Qiu (Branch Chief)
Labeling: Vicky Borders-Hemphil
Product Quality Team Lead: Jennifer Swisher
Microbial QAL: Reyes Candau-Chacon
RBPM: Keith Olin
Application Team Lead: Jennifer Swisher and Kathleen Clouse (Branch Chief)

CMC Statistics: Chao Wang, Meiyu Shen

Pharm/Tox: Wei Chen and Haleh Saber (TL)

Clinical Pharmacology: Christy John and Sarah Schrieber (TL)

Clinical Reviewers: Jennifer Gao

Statistics: Erik Bloomquist and Shenghui Tang (TL)

OSI: Lauren Iacono-Connor and Susan Thompson

OSIS: Shieh Nkah (PM)

OSE/DMEPA: Tingting Gao and Chi-Ming (Alice) Tu (TL)

OSE/DEPI: Steven Bird and Carolyn Mccloskey (TL)

DDMAC: Kevin Wright

TBBS: Leah Christl, Sue Lim, Michele Dougherty, Tyree Newman, Neel Patel, Leila Hann

Safety: Christina Marshall (PM) and Kathy Fedenko (DDS)

RPM: Leyish Minie and Christie Cottrell (TL)

DOP1 Division Director: Julia Beaver

1. Introduction

On May 30, 2017, the applicant submitted a biologics license application (BLA) under Section 351(k) of the Public Health Service Act for CT-P6, a proposed biosimilar to US-licensed Herceptin (trastuzumab)[2]. The Applicant is seeking licensure of CT-P6 for the same indications as US-Herceptin:

Adjuvant breast cancer:

d. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
e. With docetaxel and carboplatin
f. As a single agent following multi-modality anthracycline based therapy

Metastatic breast cancer (MBC):

c. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
d. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Metastatic gastric cancer:

b. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease

Section 351(i) of the Public Health Service Act (PHS Act) defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the proposed biosimilar and the reference product in terms of the safety, purity, and potency of the product." Both parts of the statutory definition must be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a determination that the products are highly similar.

The applicant conducted an analytical comparison between the proposed biosimilar and US-licensed Herceptin (henceforth referred to as US-Herceptin) to support the demonstration that the products are highly similar. The applicant also conducted a head-to-head comparison of the non-clinical PK and toxicity profiles of CT-P6 and US-Herceptin via intravenous administration in cynomolgus monkeys. Further, the applicant conducted a PK similarity study, CT-P6 1.5, and a comparative clinical study, CT-P6 3.2 (henceforth referred to as study 3.2), to support the demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin.

[2] In this document, any reference to "Herceptin" should be considered a reference to US-licensed Herceptin. References to unknown sources of trastuzumab (e.g., based on historical studies) will use "trastuzumab".

In the US, Herceptin is approved as a multi-dose vial containing 420 mg of lyophilized drug product and as a single-dose vial containing 150 mg of lyophilized drug product. (b) (4) The applicant is (b) (4) seeking licensure of the 420 mg presentation.

The analytical data supports the determination that CT-P6 is highly similar to US-Herceptin notwithstanding minor differences in clinically inactive components. In addition, the data submitted from the clinical development program of CT-P6 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. Together, the analytical and clinical data thus support the demonstration of biosimilarity of CT-P6 to US-Herceptin, as summarized below.

CT-P6 was evaluated and compared to US-Herceptin using multiple orthogonal physicochemical and functional methods. The analytical similarity data support the conclusion that the two products are highly similar, notwithstanding minor differences in clinically inactive components. The data indicate that the amino acid sequences of CT-P6 and US-Herceptin are the same. The results from the analysis of the secondary and tertiary structures and the biological activity analyses met the predefined analytical similarity acceptance criteria. Differences in the levels of some glycosylation species were identified; however, those differences did not impact biological activity in vitro and in vivo and do not preclude a finding that CT-P6 is highly similar to US-Herceptin.

However, the manufacturing and control data submitted in this application are not sufficient to support a conclusion that the manufacture of CT-P6 is well controlled and will lead to a product that is pure and potent for the duration of the shelf -life. Additional facility deficiencies have also been noted in the OPQ review.

The nonclinical pharmacokinetic and toxicity profile of CT-P6 was compared head-to-head with US-Herceptin via intravenous administration in cynomolgus monkeys. Overall, the animal studies provided in the BLA submission did not identify any safety concerns with CT-P6 or differences in the PK or toxicity profile of CT-P6 compared to US-Herceptin. The Pharmacology and Toxicology discipline has not identified any residual uncertainties.

The pharmacokinetic profiles of CT-P6 and US-Herceptin were evaluated in healthy male subjects in study CT-P6 1.5. The results of this pharmacokinetic similarity study support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. The results of this study also contribute to the totality of the data in support of a demonstration of biosimilarity of CT-P6 to US-Herceptin.

The results of study 3.2 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. Specifically, the 90% confidence intervals for the pathologic complete response rate (pCR) ratio between CT-P6 and US-Herceptin are within the pre-specified statistical equivalence margins. The safety analyses in study 3.2 did not show any meaningful differences in safety between arms.

Anti-drug antibodies were measured in study 3.2 comparing CT-P6 to US-Herceptin. The data indicate that there is no increase in immunogenicity risk in terms of ADA development for CT-P6 when compared to US-Herceptin, which supports the demonstration of no clinically meaningful differences to US-Herceptin.

The applicant provided adequate scientific justification for extrapolation of data to support licensure of CT-P6 under Section 351(k) as a biosimilar for the conditions of use for which US-Herceptin has been previously approved.

In considering the totality of the evidence, the data submitted by the applicant show that CT-P6 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between CT-P6 and US-Herceptin in terms of safety, purity and potency (safety and efficacy); however, due to manufacturing and control deficiencies, described in further detail in section 3 of this review, the application is not recommended for approval.

2. Background

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety, purity, and potency of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product specific nonclinical and clinical data.

Section 351(k) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity and potency of the proposed product in each indication based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both standalone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

The "totality of the evidence" submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes comparative

structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed biosimilar product with the US-licensed reference product.

Regulatory History

December 19, 2013: Biosimilar Biological Product Development (BPD), Type 2 Meeting

- Discussed FDA's position that the 2-way analytical similarity assessment between CT-P6 and US-licensed Herceptin is not sufficient to support a demonstration of biosimilarity, and that determination of analytical similarity will be a review issue; that a 3-way scientific bridge between EU-Herceptin, US-Herceptin, and CT-P6 would not be needed if only US-Herceptin was used as the active comparator and there is no need to rely on any data generated using EU-Herceptin to support approval; FDA clarified that all patients who received neoadjuvant therapy should receive adjuvant HER2 therapy post-operatively; primary analysis should be based on pCR rate ratio and equivalence margins calculated based on this ratio; FDA clarified that an equivalence design should be used for study 3.2; clarification on scientific justification for extrapolation was provided.

March 21, 2017: BPD, Type 3 Meeting

- Discussed pre-specified equivalence margins and 90% CI for pCR; FDA agreed to exclusion of 13 patients from one GCP non-compliant site; FDA agreed with pCR definition and that the per-protocol set should be used as primary endpoint analysis; sensitivity analyses should be conducted on a subset of the intention-to-treat (ITT) population which excludes patients from the GCP non-compliant site; Celltrion will submit 1 year of clinical data in the initial application and 20 months median follow up for safety/immunogenicity at the Day 120 Safety Data Update.

May 30, 2017: BLA 761091 submitted to FDA.

3. CMC/Device

Source: CMC/Quality/Micro/Facilities Review Team, CMC Executive Summary dated February 8, 2018; OPQ Drug Product Microbiology Review dated January 19, 2018; OPQ Product Quality Microbiology Review and Evaluation dated February 21, 2018

Discipline	Reviewer	Branch/Division
Drug Substance	Riley Myers	OPQ/OBP/DBRR I
Drug Product	Shadia Zaman	OPQ/OBP/DBRR I
Drug Substance Microbiology Drug Product Microbiology	Scott Nichols Candace Gomez-Broughton	OPQ/OPF/DMA IV OPQ/OPF/DMA IV
Facility	Thuy Thanh Nguyen	OPQ/OPF/DIA

Immunogenicity assay	Shadia Zaman	OPQ/OBP/DBRR I
Analytical Similarity	Riley Myers	OPQ/OBP/DBRR I
Labeling	Vicky Borders Hemphill	OPQ/OBP
Product quality Team Lead Microbiology QAL Facility Branch Chief	Jennifer Swisher Reyes Candau-Chacon Peter Qiu	OPQ/OBP/DBRR I OPQ/OPF/DMA IV OPQ/OPF/DIA
CMC RPBM	Keith Olin	OPQ/OPRO
Application Team Lead	Jennifer Swisher	OPQ/OBP/DBRR I

Final Product Quality Team Recommendation: Complete Response

General product quality considerations

Trastuzumab targets human epidermal growth factor receptor 2 (HER2) and when bound to HER2 on HER2-expressing cells, trastuzumab 1) inhibits HER2 receptor dimerization and downstream signaling, 2) increases destruction of the endocytic portion of the HER2 receptor 3) inhibits HER2 extracellular domain shedding, and 4) activates cell-mediated immune defenses such as ADCC activity through concomitant binding to Fcγ receptors on immune effector cells.

CT-P6 is a humanized IgG1κ monoclonal antibody produced in CHO cells. CT-P6 drug product is manufactured to the same strength and presentation as U.S.-licensed Herceptin at 420 mg/vial; the formulation is identical except for an increase in α,α-trehalose dihydrate (from 381 to 839 mg/vial), which is a (b) (4). CT-P6 drug product is supplied at 420 mg/vial as a sterile, lyophilized powder for intravenous infusion; the 420 mg presentation is a multi-dose vial. CT-P6 is proposed as a treatment for HER2-overexpressing breast cancer and gastric cancer.

CT-P6 monoclonal antibody consists of two heavy chains that are each composed of 450 amino acids and two light chains that are each composed of 214 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 300 (Asn300). The molecular weight of CT-P6 without C-terminal lysine is 148,055 Da. The theoretical extinction coefficient was calculated to be 1.48 (mg/mL) -1 cm-1, and it was determined experimentally to be 1.44 (mg/mL) -1 cm-1. The theoretical value has been used during development and will continue to be used to determine the CT-P6 protein concentration for commercial use.

CT-P6 is produced in genetically engineered CHO (b) (4) cells. The CT-P6 Master Cell Bank (MCB, CTC-06M-247) was developed through (b) (4) The Working Cell Bank (WCB, MCB, CTC-06W-247) was created by the expansion of the MCB. This two-tiered cell banking system was implemented to ensure continued source of product. Non-animal derived materials were used in the manufacture of the WCB. The cell lines were appropriately tested to ensure product safety from adventitious and endogenous agents. Viability of both the MCB and WCB is monitored as part of a stability program.

CT-P6 drug substance is manufactured at Celltrion Inc., Incheon, Republic of Korea. (b) (4)

(b) (4)

The CT-P6 drug substance manufacturing process development is based on minimal process characterization and process validation studies (see details in the CMC executive summary and specific discipline reviews). The overall adequacy of the control strategy cannot be assessed in the absence of a pre-license inspection, which could not take place during this review cycle.

CT-P6 drug product manufacturing includes (b) (4)
(b) (4)
(b) (4) The control strategy is inadequate (see details in CMC Executive Summary and CR items below).

The bacteriostatic water for injection (BWFI) manufacturing process includes (b) (4)

The OPQ reviewers provided the following recommendations and conclusion:

- The data submitted in this application are not sufficient to support a conclusion that the manufacture of CT-P6 is well controlled and will lead to a product that is pure and potent for the duration of the shelf -life. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Celltrion to describe the deficiencies noted and the information and data that will be required to support approval.

- Additionally, this application cannot be approved during this review cycle due to facility deficiencies. (b) (4) The Division of Inspectional Assessment, OPF, OPQ is recommending a withhold status, and a Complete Response letter be issued to Celltrion to describe the deficiencies noted.

- Pending the pre-license inspection that may include an on-site assessment of similarity data, the analytical similarity assessment is adequate to support the conclusion that the biological product, CT-P6, is highly similar to US-Herceptin.

Microbiology reviews

Dr. Scott Nichols (DS microbiology review) recommended approval of the BLA, as amended, from a microbial control and a microbiological product quality perspective.

Drs. Candace Gomez-Broughton (DP and BWFI microbiology review) recommended approval of the BLA from an assessment of sterility assurance and microbiology product quality perspective.

Facilities review/inspection

Facilities review was performed by Thuy T. Nguyen, OPF/DIA, with concurrence from branch chief Zhihao Peter Qiu. Adequate descriptions were provided for the CT-P6 DS and DP at the Celltrion facility but the Division of Inspectional Assessment, OPF, OPQ was unable to conduct a pre-license inspection in support of this BLA for the following reason. A surveillance inspection was conducted at the Celltrion, Inc. facility in Incheon, Republic of Korea, from May 22 – June 02, 2017 which resulted in an Official Action Indicated (OAI) status with Warning Letter Recommendation. The Warning Letter was issued to Celltrion on January 26, 2018. A pre-licensing inspection cannot be conducted until the OAI status is cleared by OMQ. Master Cell Bank and testing facilities for DS and DP are acceptable. The Celltrion Inc., Incheon, Republic of Korea facility is recommended for WITHHOLD from a facilities assessment standpoint.

Analytical similarity assessment

The analytical similarity assessment was performed to demonstrate that CT-P6 and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components.

CT-P6 was evaluated and compared to US-Herceptin using a battery of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action (see Section II A, CMC Executive Summary). The analytical data submitted support the conclusion that CT-P6 is highly similar to US-Herceptin. The amino acid sequences of CT-P6 and US-Herceptin are identical. A comparison of the secondary and tertiary structures and the impurity profiles of CT-P6 and US-Herceptin support the conclusion that the two products are highly similar.

Inhibition of proliferation, and ADCC activity, which reflect the presumed primary mechanisms of action of trastuzumab, were determined to be equivalent. HER2 binding is similar between CT-P6 and US-Herceptin. Some tests indicate that small shifts in low abundance glycan forms [e.g., sialic acid, high mannose, and non-glycosylated heavy chain (NGHC)] exist and are likely an intrinsic property of CT-P6 due to the manufacturing process. High mannose and sialic acid containing glycans can impact PK, while NGHC is associated with loss of effector function through reduced FcγRIIIa binding and reduced ADCC activity. However, ADCC activity was similar and FcγRIIIa binding was similar between CT-P6 and US-Herceptin. The minor differences related to the increase in total mannose forms and NGHC and decrease in sialic acid were addressed by the ADCC similarity and by the PK similarity between CT-P6 and US-

Herceptin as concluded by the clinical review team. Additional subtle differences in size and charge related variants were detected; however, these variants generally remain within the quality range criteria. Further, the data submitted by the applicant support the conclusion that CT-P6 and US-Herceptin can function through the same mechanisms of action for the indications for which US-Herceptin is currently approved, to the extent that the mechanisms of action are known or can reasonably be determined. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, CT-P6 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components. CT-P6 meets the statutory "same strength" requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

Reviewer Comment: I concur with the CMC/OPQ review team's conclusion that the analytical data supports a determination that CT-P6 is highly similar to US-Herceptin. However, because of manufacturing and control deficiencies as well as facility deficiencies, this application is not recommended for approval. Refer to the finalized list of Complete Response comments in the CR Letter forwarded to the applicant on March 29, 2018.

CDRH

CDRH consultation was requested pertaining to the product label for BLA 761091, under sections 1.1, 1.2, and 1.3, regarding the statement for the companion diagnostic. Per CDRH reviewers (Drs. Jacob Richards, Eunice Lee, and Reena Philip), CDRH agreed with the CDER review team that the label should indicate the following: "Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product."

The applicant was requested to provide a rationale for why the approved companion diagnostics for trastuzumab could serve as companion diagnostics for CT-P6. The applicant provided a response on January 19, 2018. CDRH reviewers concluded that Celltrion's response explaining why it believes the approved companion diagnostics for trastuzumab could serve as companion diagnostics for CT-P6 is adequate. Moreover, for purposes of the HER-2 tests approved as companion diagnostics for trastuzumab, CDRH believes that reference to trastuzumab in the device labeling includes not only Herceptin but also products determined to be biosimilar to Herceptin.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology primary Review dated February 20, 2018 (Drs. Wei Chen and Haleh Saber)

Final Pharmacology/Toxicology Team Recommendations: Approval.

A 4-week study with weekly administration of CT-P6 and US-licensed Herceptin were conducted in monkeys to compare the toxicity profiles and the toxicokinetic (TK) profiles of CT-P6 and US-licensed Herceptin. Monkey has been identified as a pharmacologically relevant

species. CT-P6 or US-licensed Herceptin was administered to cynomolgus monkeys at doses of 0 (Control), 14 and 42 mg/kg/week on Days 1, 8, 15 and 22. No apparent toxic response was observed in monkeys treated with CT-P6 or US licensed Herceptin at doses up to 42 mg/kg, which was consistent with published data for US-licensed Herceptin. TK evaluation showed that animals were continuously exposed to CT-P6 or US-licensed Herceptin for the duration of the study. Following repeated administration of CT-P6 and US licensed Herceptin at 14 and 42 mg/kg, similar systemic exposures were observed for both products. Accumulation of CT-P6 drug product and US-licensed Herceptin in serum was observed with repeated dosing over the 4-week dosing period. No immunogenic (anti-drug antibodies) responses to CT-P6 or US-licensed Herceptin were detected in samples taken from treated animals.

The pharmacology/toxicology review team recommended approval.

Reviewer Comment: I concur with nonclinical team's conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the toxicity and TK profiles of CT-P6 and US-Herceptin in cynomolgus monkeys.

5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Christy S. John, Thiengi M. Thway, Sarah J. Schrieber and Nam Atiqur Rahman) and immunogenicity analysis from Dr. Shadia Zaman)

Final Clinical Pharmacology Team Recommendations: Approval

The objectives of the clinical pharmacology program were to demonstrate pharmacokinetic (PK) similarity between CT-P6 and US-Herceptin. The Applicant submitted study CT-P6 1.5 which evaluated the PK of CT-P6 and US-Herceptin.

Study CT-P6 1.5 was a single-dose, randomized, double-blind, 2-arm, parallel group study in 70 healthy male subjects designed to demonstrate PK similarity of CT-P6, and US-licensed Herceptin following a single 6 mg/kg intravenous dose infused over 90 minutes. The 90% confidence intervals (CI) for all pairwise comparisons of the PK endpoint (AUC0-inf) were within the limits of 80 to 125%. The results of the study established PK similarity between CT-P6 and US-licensed Herceptin. Overall, Study CT-P6 1.5 supports a demonstration of PK similarity between CT-P6 and US-licensed Herceptin.

Immunogenicity

The incidence of immunogenicity for CT-P6 and US-licensed Herceptin was compared in a multiple-dose, parallel-arm study in 562 patients with early HER2 positive breast cancer (CT-P6 3.2). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. These data indicate that there is no increase in immunogenicity risk for CT-P6 as compared to US-licensed Herceptin.

In conclusion, the PK and immunogenicity results support a demonstration of no clinically meaningful differences between CT-P6 and US-licensed Herceptin and add to the totality of the evidence to support a demonstration of biosimilarity of CT-P6 and US-licensed Herceptin.

Reviewer Comment: I concur with clinical pharmacology team's conclusion that the submitted clinical pharmacology study adequately demonstrated PK similarity between CT-P6 and US-Herceptin. The evidence of PK similarity supports a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. The immunogenicity data indicate that there is no increase in immunogenicity risk for CT-P6 when compared to US-Herceptin, which supports a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Combined Clinical/Stat Review (Drs. Jennifer Gao, Erik Bloomquist and Shenghui Tang)

Final Clinical/Statistical Team Recommendations: Approval

The applicant also submitted study CT-P6 3.2 to support a determination of no clinically meaningful differences between CT-P6 and US-Herceptin.

Study 3.2 is a double-blind, randomized, parallel-group clinical study to compare the efficacy and safety of CT-P6 and US-Herceptin in the neoadjuvant and adjuvant treatment of patients with early HER2 positive breast cancer. In the neoadjuvant portion, patients were treated with 4 cycles of CT-P6 plus docetaxel or US-Herceptin plus docetaxel followed by 4 cycles of CT-P6 or US-Herceptin with 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy. In the adjuvant portion, CT-P6 or US-Herceptin was continued to complete 1 year of trastuzumab-based therapy (up to 10 cycles during the adjuvant portion). See Figure 1, below. Patients were randomized 1:1 and stratified by disease stage (stage I or II vs. IIIa), estrogen/progesterone receptor status (positive vs. negative); country of treatment was an additional geographic stratification factor.

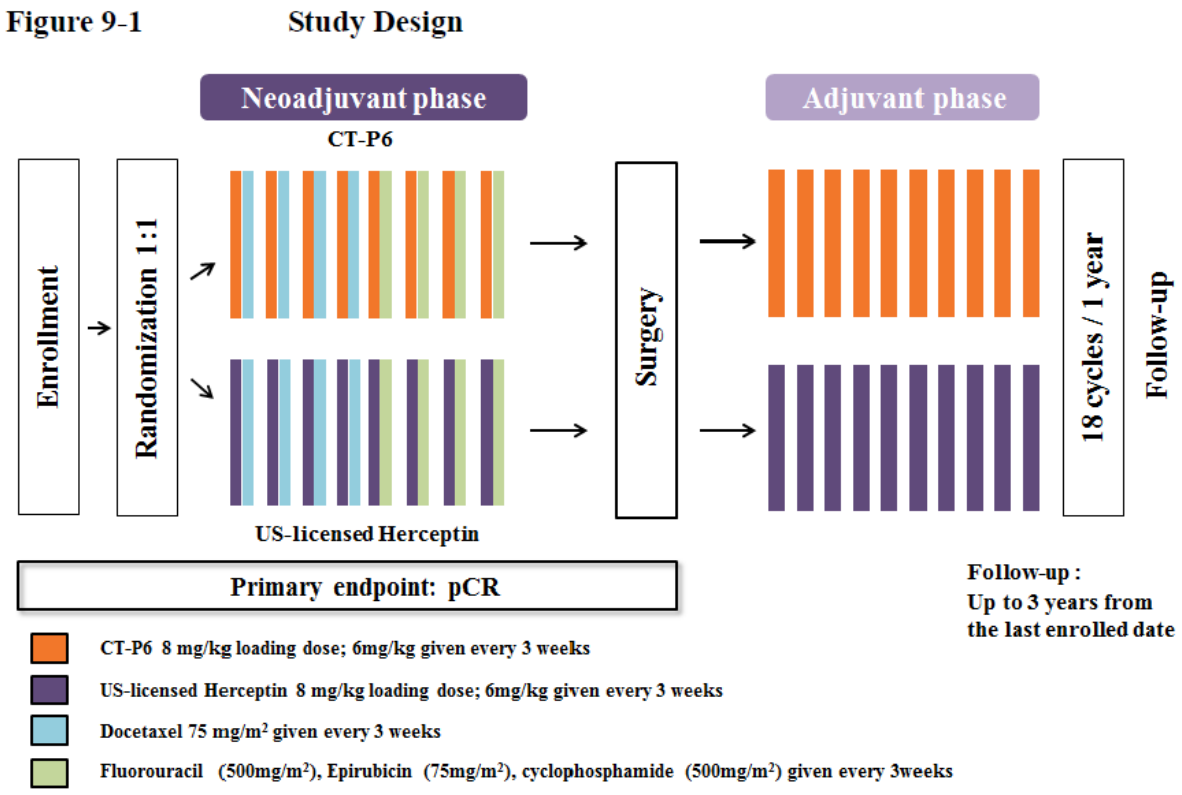

Figure 1. CT-P6 3.2 Study Schema
Source: CT-P6 3.2 Clinical Study Report

The primary efficacy endpoint of this trial was pathological complete response (pCR), defined as the absence of invasive tumor cells in the breast and in axillary lymph nodes, regardless of DCIS. The pCR was determined at the time of surgery, using hematoxylin and eosin evaluation of the resected breast specimen. The applicant used the 90% asymptotic confidence region of the ratio of pCR in the CT-P6 arm vs. the US-Herceptin arm as the primary analysis strategy. The primary analysis population was the per-protocol set (those without major protocol violations); the intention to treat population was used for supportive purposes.

The study was deemed positive if the 90% confidence region for the ratio was entirely contained with the interval (0.75, 1.35). To calculate this interval, the applicant reviewed six study control arms to obtain pCR rates for the control arm and four study treatment arms to obtain pCR rates for the treatment arms. The overall pCR rate for their control arm was estimated to be 15.9% (14 – 18%), and the overall pCR rate for their treatment arm was estimated to be 53.7% (38-70%). Using a 50% retention rate, the sponsor derived their equivalence margin for the ratio.

The applicant sized their study to achieve 80% power for the primary endpoint. The sponsor calculated that 266 patients per arm would provide sufficient power and account for a 10% dropout.

The primary pCR data were reviewed by a blinded central committee as a sensitivity analysis. Note that only pathology reports were sent to the blinded central committee, so the agreement was 100% between the local pathology and central pathology.

Key secondary endpoints included radiological endpoints such as overall response rate using RECIST v1.1 criteria and PFS. Overall survival was also a key secondary endpoint. For the radiological endpoints, scans were done in the neoadjuvant and adjuvant periods. The local investigator determined whether an individual had a response or progression event. A central review committee was used and reviewed the radiological images and made determinations of ORR and PFS for sensitivity purposes.

The statistical analysis plan had four versions. Significant changes include a change from the risk difference to risk ratio, the use of a 90% confidence interval instead of a 95% confidence interval for the primary analysis, and the use of the per protocol population for the primary analysis.

In summary, Study 3.2, together with other information in the application including Study 1.5, supports the demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. Specifically, the 90% confidence interval for the pCR ratio between CT-P6 and US-Herceptin in Study 3.2 is within the equivalence margin.

Reviewer Comment: I concur with clinical team's conclusion that the submitted clinical study demonstrated no differences in terms of efficacy between CT-P6 and US-Herceptin. Consequently, the results of study 3.2 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin.

8. Safety

Source: Combined Clinical/Stat Review dated February 13, 2018 (Dr. Jennifer Gao)

Final Clinical/Statistical Team Recommendations: Approval

The safety evaluation for this application is based on the neoadjuvant and adjuvant study portions of study 3.2. The safety assessments for 3.2 are adequate. There was particular attention to assessment of cardiac adverse events (AEs) due to the known cardiac effects of trastuzumab. The safety population consisted of 549 patients, 271 in the CT-P6 and 278 in the US-Herceptin arms and is defined as all patients who received at least 1 dose of study drug in any amount. The 13 patients from the non-GCP compliant site 2302 were excluded from the safety population as the actual treatment given to these patients could not be confirmed.

The frequency of TEAEs, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. Major events of interest which are listed as Black Box Warnings in the prescribing information for US-Herceptin include cardiomyopathy, infusion reactions, pulmonary toxicity, and embryo-fetal toxicity. There were

no reports of embryo-fetal toxicity in study 3.2. Most cardiac adverse events were grade 1-2 and most patients recovered in both groups. The safety results of study 3.2 showed no meaningful differences between CT-P6 and US-Herceptin.

Reviewer Comment: The comparative safety results obtained in study 3.2 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. I concur with clinical team's conclusion that the submitted clinical study adequately supports a finding that there are no clinically meaningful differences in terms of safety between CT-P6 and US-Herceptin.

9. Considerations for Extrapolation of Biosimilarity

Source: Combined Clinical/Stat Review (Dr. Jennifer Gao)

The applicant seeks licensure for all indications for which US-Herceptin is licensed. The applicant has provided adequate justification for extrapolation of the data and information in the application, including comparative clinical efficacy and safety data from a clinical program in patients with early HER2 positive breast cancer, to support licensure of CT-P6 under Section 351(k) for the indications for which US-Herceptin is licensed.

The neoadjuvant setting for breast cancer used in study 3.2 is an acceptable, homogenous, and sensitive patient population to evaluate for no clinically meaningful differences between CT-P6 and US-Herceptin. The patient population receiving HER2-based treatment is the same in the neoadjuvant and adjuvant settings, differing only in the timing of surgery. The primary endpoint of pCR is an acceptable endpoint in breast cancer. The mechanism of action of trastuzumab in neoadjuvant breast cancer patients is expected to be the same as the mechanism of action for trastuzumab in the indications for which the applicant is seeking licensure. For these reasons, the study population and primary endpoint used in study 3.2 is acceptable to support approval of CT-P6 for the indications for which US-Herceptin has been previously approved.

The applicant has submitted the following scientific justifications for extrapolation of data to support licensure of CT-P6 as a biosimilar for the conditions of use for which US-Herceptin has been previously approved:

- The mechanism of action of trastuzumab is the same across all indications as the target receptor involved (HER2) is the same across indications
- The available safety data of the reference product does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population
- There are no toxicities that are related to off-target activities in patients treated in the neoadjuvant setting compared with adjuvant/metastatic breast cancer or metastatic gastric cancer
- The dose of US-Herceptin and route of administration is similar across all indications

- PK results support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin

- Immunogenicity was low and similar between CT-P6 and US-Herceptin

As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed. The applicant has demonstrated that CT-P6 is highly similar to US-Herceptin with respect to analytical attributes, and that there are no clinically meaningful differences in safety, purity, and potency, which supports approval for all indications for which US-Herceptin was previously approved (adjuvant and metastatic breast cancer and metastatic gastric cancer). The clinical team consider extrapolation to be scientifically justified based on the bullets above.

Reviewer Comment: I concur with clinical team's conclusion that the evidence indicates that the extrapolation of data, including clinical data, to support licensure of CT-P6 for the indications for which US-Herceptin has previously been approved is scientifically justified.

10. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

11. Pediatrics

Celltrion requested a full waiver of pediatric studies for the requested indications and submitted an agreed iPSP with the BLA. Breast and gastric cancers are included in FDA's September 2005 Guidance (How to Comply with the Pediatric Research Equity Act) for disease-specific waivers. The Oncology Center of Excellence Subcommittee of the Pediatric Review Committee met on January 31, 2018 and concurred with the applicant's request for a full waiver in HER-2 overexpressing breast and gastric cancers. The minutes were entered to DARRTS February 14, 2018.

12. Other Relevant Regulatory Issues

Application Integrity Policy (AIP)
The application contained statements from Celltrion that they certified that they did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Exclusivity or patent Issues

Not applicable.

Financial disclosures

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, the applicant requested statements of financial interest from 114 principal investigators (PIs) and 449 sub-investigators for studies CT-P6 1.4, 1.5, and 3.2. All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the applicant and propriety interest. The applicant has stated that none of the clinical investigators involved with the CT-P6 studies have financial interests or arrangements to disclose as defined in 21 CFR 54.2(f).

Bioequivalence Inspections

In a review entered into DARRTS on August 21, 2018, Angel S. Jonson of the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study
Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this approach was that OSIS had recently inspected two clinical and one analytical site, for which the inspectional outcomes were classified as No Action Indicated (NAI). The clinical sites previously inspected were the (b) (4) , and (b) (4) The analytical site previously inspected was (b) (4) .

Clinical Inspections

Lauren Iacono-Connors, Susan Thompson (Team Leader) and Kassa Ayalew (Branch Chief) from the Division of Clinical Compliance Evaluation, OSI, completed the clinical inspection summary (CIS) on December 8, 2017. FDA selected three clinical sites for audit. There were no significant inspectional findings for two of these three clinical investigators. There were no significant inspectional findings for clinical investigators Dr. Zanete Zvirbule, M.D., and Dr. Dmytro Boliukh, M.D. ORA recommended that the inspection of Dr. Vladimir Moiseenko, M.D. (Site 2816) be cancelled because as of December 1, 2017 the Russian Embassy had not yet responded to a visa request from ORA for the FDA field investigator. The inspection was cancelled on December 1, 2017. OSI review concluded that the data from study CT-P6 3.2

submitted to the Agency in support of BLA 761091, appear reliable based on available information.

Other Discipline Consultations

Tingting Gao and Chi-Ming (Alice) Tu from the Office of Medication Error Prevention and Risk Management (OMEPRM) completed a review dated August 14, 2017, that concluded that the proposed proprietary name, Herzuma, was conditionally acceptable. On February 14, 2018, the reviewers affirmed that the proprietary name was also conditionally acceptable following the [redacted] (b) (4).

Tingting Gao and Lubna Merchant from OMEPRM completed a review dated July 19, 2017 that determined that the suffix [redacted] (b) (4) derived from [redacted] (b) (4) for the proper name is conditionally acceptable (trastuzumab-[redacted] (b) (4)

Tingting Gao and Chi-Ming (Alice) Tu completed a review dated March 6, 2018 that defined recommendations relating to carton and container and product labeling. The recommendations were incorporated in revised product labeling.

Pediatric and Maternal Health

At the time of the submission of this BLA, a pregnancy registry and pharmacovigilance program was in place for US-Herceptin. Because the risks of oligohydramnios have been adequately characterized in the Herceptin labeling, FDA has determined that the Herceptin pregnancy registry and pregnancy pharmacovigilance program are no longer necessary for Herceptin and therefore, no registry or pharmacovigilance program is required for this biosimilar. Additional details may be found in the primary clinical review.

13. Labeling

Proposed labeling submitted by Celltrion was generally consistent with recommendations contained within FDA's draft Guidance for Industry "Labeling for Biosimilar Products" which recommends that the biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product specific modifications. Some information in the labeling was revised to reflect CT-P6-specific information as well as to comply with current labeling practices. The review teams reserve final comment on the proposed labeling, container labels, and carton labeling until the application is otherwise adequate.

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The applicant is seeking licensure for indications that are the same as those licensed for US-Herceptin. The applicant is seeking licensure for the adjuvant treatment of HER-2 overexpressing breast cancer, treatment of HER-2 overexpressing metastatic breast cancer, and treatment of HER-2 overexpressing metastatic gastric cancer indications. The data submitted to the BLA from the clinical development program of CT-P6 support a demonstration of no clinically meaningful differences between CT-P6 and US-Herceptin. These data also contribute to the totality of the data in support of a demonstration of biosimilarity of CT-P6 to US-Herceptin. The applicant provided adequate scientific justification for extrapolation of data to support licensure of CT-P6 for the breast cancer and metastatic gastric cancer indications. The applicant demonstrated that CT-P6 is highly similar to US-Herceptin based on extensive analytical data and that CT-P6 has no clinically meaningful differences from US-Herceptin in terms of safety, purity and potency. Accordingly, the data submitted support licensure of CT-P6 as biosimilar to US-Herceptin.

However, because of the inspectional and product quality deficiencies identified by OPQ, as summarized in section 3 of this review, the 351(k) BLA 761091 for CT-P6 will not be recommended for approval. Specifically, the data submitted in this application were not found to be sufficient to support a conclusion that the manufacture of CT-P6 is well controlled and will lead to a product that is pure and potent for the duration of the shelf -life. Additionally, this application cannot be approved during this review cycle due to facility deficiencies.

Risk Benefit Assessment

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” Both parts of the statutory definition must be met to establish biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

As explained above, the data submitted to the 351(k) BLA support licensure of CT-P6 as biosimilar to US-Herceptin under section 351(k) of the PHS Act. Accordingly, CT-P6 is considered to have a favorable risk-benefit profile for all requested conditions of use.

However, because of the inspectional and product quality deficiencies identified by OPQ, as summarized in section 3 of this review, this application is not recommended for approval.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

None.

Recommended Comments to Applicant

See Section 3, Chemistry, Manufacturing, and Controls for the list of CMC deficiencies and comments to be communicated to the applicant.

Recommended Regulatory Action

Complete Response.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANJEEVE BALASUBRAMANIAM
03/29/2018

JULIA A BEAVER
03/29/2018