CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761100Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	December 21, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761100
Product Name and Strength:	Ontruzant (trastuzumab-dttb) for Injection, 150 mg/vial
Applicant/Sponsor Name:	Samsung Bioepis Co., Ltd
FDA Received Date:	December 20, 2018
OSE RCM #:	2017-2168-3
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container label and carton labeling for Ontruzant (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling for Ontruzant are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Gao, T. Memorandum Review of Revised Label and Labeling for Ontruzant (BLA 761100). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 19. RCM No.: 2017-2168-2.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 20, 2018

Container labels

(b) (4)

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/s/

TINGTING N GAO
12/21/2018

DANIELLE M HARRIS
12/21/2018

MEMORANDUM

REVIEW OF LABEL AND LABELING

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)

Date of This Memorandum:	December 19, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761100
Product Name and Strength:	Ontruzant (trastuzumab-dttb) for Injection, 150 mg/vial
Applicant/Sponsor Name:	Samsung Bioepis Co., Ltd
FDA Received Date:	August 13, 2018
OSE RCM #:	2017-2168-2
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

This memo amends our previous review[a] of the proposed container labels and carton labeling for BLA 761100 (Appendix A). This amendment is in response to the General Advice Letter issued to Samsung Bioepis on August 9, 2018[b] that designated a four-letter distinguishing suffix, -dttb, for inclusion in the proper name for BLA 761100 and communicates our recommendations to incorporate the nonproprietary name into the container label and carton labeling.

2 REGULATORY HISTORY

On January 13, 2017, FDA issued final guidance entitled Nonproprietary Naming of Biological Products stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning. [c]

[a] Gao, T. Memorandum Review of Revised Label and Labeling for Ontruzant (BLA 761100). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Aug 16. RCM No.: 2017-2168-1.
[b] Harris, D. General Advice Letter for BLA 761100. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 2018 Aug 9.
[c] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

On October 20, 2017, Samsung Bioepis submitted a list of 5 suffixes, in their order of preference, to be used in the nonproprietary name of their product[d].

On July 10, 2018, we found the nonproprietary name, trastuzumab-dttb, conditionally acceptable for BLA 761100.[e]

On August 9, 2018, our recommendations to revise the proposed labels and labeling accordingly were communicated to Samsung Bioepis in a General Advice letter.[f]

3 DISCUSSION

The container label and carton labeling for BLA 761100 are not acceptable from a medication error perspective because the proper name lacks the FDA-designated nonproprietary name suffix, -dttb, appended to the core name, trastuzumab.

4 RECOMMENDATIONS FOR SAMSUNG BIOEPIS

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (All Labels and Labeling)

a. Revise the nonproprietary name on all container label and carton labeling to incorporate the FDA-designated nonproprietary name suffix, -dttb, appended to the core name, trastuzumab so that the nonproprietary name appears as trastuzumab-dttb throughout the labels and labeling. Submit the revised container label and carton labeling for our review.

On August 9, 2018, our recommendations to revise the proposed labels and labeling to incorporate the FDA-designated nonproprietary name, trastuzumab-dttb, were communicated to you in a General Advice letter.

[d] Suffix Name Request. BLA 761100. Incheon (Republic of Korea): Samsung Bioepis Co., Ltd.; 2017 OCT 20. Available from: \\cdsesub1\evsprod\bla761100\0001\m1\us\118-prop-names\sb3-us-1-18-suffix-name-request.pdf

[e] Gao, T. Nonproprietary Name Suffix Memorandum for trastuzumab-dttb (BLA 761100). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 July 10. RCM No.: 2017-2169.

[f] Harris, D. General Advice Letter for BLA 761100. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 2018 Aug 9.

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12/19/2018

DANIELLE M HARRIS
12/19/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	August 16, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761100
Product Name and Strength:	Ontruzant (trastuzumab-dttb) for Injection, 150 mg/vial
Applicant/Sponsor Name:	Samsung Bioepis Co., Ltd
FDA Received Date:	August 13, 2018
OSE RCM #:	2017-2168-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container label and carton labeling for Ontruzant (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

The Applicant proposed to use YYYYMMMDD (e.g., 2017JAN31) as the expiration date format instead of the previously recommended format similar to either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017) on the container label and carton labeling for the following reasons:[b]

> First, the Applicant believes indication of the day in the expiration date is necessary to inform health care professionals at what part of the given month (i.e., beginning, middle, or the end) the expiry will occur. Second, by placing the MMM between the numeric year and day, the format YYYYMMMDD helps avoid confusion regarding which part of the number indicates the year and which part indicates the day.

Since the proposed numerical expiration date format consists the full year (YYYY), which would not be confused with the day (DD), we find this proposed expiration date format acceptable from a medication error perspective.

Furthermore, the Applicant clarified the intent of repeating the LOT and EXP statements three times on the container label:[b]

> In addition to the one LOT and EXP statement in the middle that is affixed to the vial container, two more LOT and EXP statements (above and below the affixed lot and expiration date) that can be peeled off and attached onto, for example infusion bags, are included to reduce possible medication errors. Therefore, as the Applicant was able to secure space to accommodate all labeling recommendations by the Agency, the Applicant intends to maintain the multiple LOT and EXP statements.

We note the Applicant also utilizes one affixed and two peel off LOT and EXP statements on their other product (e.g., Renflexis), and recognize that the peel off may assist nurses in documentation on paper medical administration records. Thus, we find this proposal acceptable from a medication error perspective.

3 CONCLUSION

The revised container label and carton labeling for Ontruzant are acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Gao, T. Label and Labeling Review for Ontruzant (BLA 761100). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 11. RCM No.: 2017-2168.

[b] BLA 761100. eCTD Sequence No. 0025. SB3 (a proposed biosimilar to Herceptin®). Response to Information Request. Incheon (Republic of Korea): Samsung Bioepis Co., Ltd. 2018 AUG 13. Available at \\cdsesub1\evsprod\bla761100\0025\m1\us\labeling-response.pdf.

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/s/

TINGTING N GAO
08/16/2018

CHI-MING TU
08/16/2018

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

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

Memorandum

Date: August 9, 2018

To: Julia Beaver, M.D., Director
Division of Oncology Products 1 (DOP1)

Janice Kim, 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: Trung-Hieu (Brian) Tran, PharmD, M.B.A., Team Leader, OPDP

Subject: OPDP Labeling Comments for SB3 (trastuzumab-xxxx)

BLA: 761100

In response to DOP1's consult request dated November 16 and November 21, 2017, OPDP has reviewed the proposed product labeling (PI), container label and carton labeling for the original BLA submission for SB3 (trastuzumab).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1 (Janice Kim) on August 8, 2018, and 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 October 20, 2017, 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.

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/s/

KEVIN WRIGHT
08/09/2018

Clinical Inspection Summary

Date	July 19, 2018
From	Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation
To	Janice Kim, Regulatory Project Manager Tatiana Prowell, Clinical Reviewer Division of Oncology Products 1
BLA #	761100
Applicant	Samsung Bioepis Co., Ltd.
Drug	SB3 (trastuzumab-biosimilar[Bs])
NME	Biosimilar
Therapeutic Classification	Biosimilar to U.S.-licensed Herceptin: HER2 receptor inhibitor
Proposed Indication	Adjuvant Breast Cancer, Metastatic Breast Cancer, Metastatic Gastric Cancer
Consultation Request Date	December 20, 2017 (Submission date: October 20, 2017)
Summary Goal Date	August 15, 2018
Action Goal Date	October 17, 2018
BsUFA Date	October 20, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study SB3-G31-BC was submitted to the Agency in support of BLA 761100. Three clinical sites, Dr. Seock-Ah Im, M.D. (Site 104), Dr. Maximino Bello, M.D. (Site 903), Dr. Tomasz Sarosiek, M.D. (Site 1010), and the study sponsor, Samsung Bioepis Co., Ltd., were selected for audit.

There were no significant inspectional findings for clinical investigators Dr. Seock-Ah Im, Dr. Maximino Bello, Dr. Tomasz Sarosiek, and the study sponsor, Samsung Bioepis Co., Ltd. The data from Study SB3-G31-BC submitted to the Agency in support of BLA 761100, appear reliable.

II. BACKGROUND

Samsung Bioepis Co., Ltd. (Samsung), as sponsor of BLA 761100, seeks approval to market SB3, a proposed biosimilar to US-licensed Herceptin® (trastuzumab, Genentech Inc.). The key clinical study supporting this application is Study SB3-G31-BC.

The following overview of the Study SB3-G31-BC is intended as background context for interpreting the inspectional findings.

Study SB3-G31-BC was conducted at 97 study centers worldwide, including the United States. These study centers screened 1254 subjects and 875 were randomized (437 subjects and 438 subjects in the SB3 and U.S.-licensed Herceptin treatment groups, respectively)

The study was conducted under IND 123158.

Study SB3-G31-BC, is entitled, "A Phase III Randomized, Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB3 (proposed trastuzumab biosimilar) and Herceptin® in Women with Newly Diagnosed HER2 Positive Early or Locally Advanced Breast Cancer in Neoadjuvant Setting"

Study Period: Date of first subject enrolled: April 14, 2014
Last Subject/last visit: February 14, 2017

Primary efficacy endpoint: Pathological complete response (pCR), defined as no histological evidence of residual invasive tumor cells in the breast specimen removed at surgery [breast pCR; bpCR].

Objectives of Inspections:

a. Verify select efficacy endpoint variables as determined by the clinical investigator
    - pCR
    - Total pathological complete response (tpCR) rate, defined as the absence of invasive residual tumor cells in both breast and lymph nodes.
b. Verify OS
c. Identification, documentation, and reporting of adverse events (AEs)
d. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI: Dr. Seock-Ah Im, M.D. (Site 104) 101 Daehak-ro Jongno-gu Seoul, NA 3080 Republic of Korea	Protocol: SB3- G31-BC Subjects: 26	March 26-29, 2018	NAI
CI: Dr. Maximino Bello, M.D. (Site 903) St. Luke's Medical Center E. Rodriguez Sr. Boulevard Quezon City, 1102 Philippines	Protocol: SB3- G31-BC Subjects: 18	April 30, 2018 to May 4, 2018	NAI
CI: Dr. Tomasz Sarosiek, M.D. (Site 1010) Fieldorfa 40 Warszawa, NA 04-125 Poland	Protocol: SB3- G31-BC Subjects: 20	April 16-20, 2018	NAI

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
Sponsor: Samsung Bioepis Co., Ltd. Building 4, 130, Samsung-ro, Yeongtong-gu Suwon-si, Gyeonggido, 16678, Republic of Korea	Protocol: SB3- G31-BC Site Numbers: 104, 1010, 1113, 1215, and 1612	April 2-6, 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Seock-Ah Im, M.D. (Site 104)

The site screened 27 subjects and randomized 26 subjects. A record review was done for all 27 subjects. The 26 enrolled subjects were randomized during the period of April 2014 through August 2015. Three subjects had discontinued participation in the study; Subjec (b) (6) had died by suicide, Subject (b) (6) withdrew consent due to a serious adverse event, and Subject (b) (6) had discontinued due to progressive disease and recurrence. There were 23 subjects that had completed the study treatment period. At the time of the inspection, the study had completed the treatment phase and the subjects are currently participating in the long-term 5-year safety follow-up period.

Review of all 27 screened subjects' and 26 enrolled subjects' records revealed that one subject (Subject (b) (6)) had failed to initially consent to participate in the pharmacokinetic (PK) substudy. However, PK samples were collected from Subject (b) (6) on Cycle 1 Day 1 (C1D1) 10/29/2014, C3D1 12/09/2014, and C8D1 03/31/2015. Subject (b) (6) was reconsented to the study and consented to participate on the PK substudy after PK samples had been collected.

OSI Reviewer Note: Dr. Im stated that Subject (b) (6) had verbally consented to the PK substudy at the time of initial consent. Dr. Im also stated, during the close out meeting, that she understood the importance of documenting the consent at the same as obtaining (verbal) consent for a study subject and pointed out that the subject had consented to participating in the PK substudy after re-consenting to the study. Dr. Im promised to develop and implement corrective and preventive actions to mitigate the inspection observation moving forward.

Excluding the failure to obtain Subject (b) (6) consent for PK substudy participation, all subjects met eligibility criteria and were appropriately consented prior to study participation.

Key data points found in the source documents for the 26 randomized subjects were compared to the data line listings submitted to the application, including pathological complete response (pCR), total pathological complete response (tpCR), AEs and SAEs, protocol deviations, subject discontinuations, concomitant medications, and randomization. All randomized subjects were properly followed per the study protocol. No data discrepancies were identified and all subject records and IP accountability records were complete. Institutional Review Board (IRB)/Ethics Committee (EC) approvals were appropriately obtained. The IRB/EC was appropriately notified of SAEs, study deviations, safety notifications, and Data Safety Monitoring Board (DSMB) outputs.

The inspection revealed no significant deficiencies. The primary efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

2. Dr. Maximino Bello, M.D. (Site 903)

The site screened 23 subjects and randomized 18 subjects. A record review was done for all 18 subjects. At the time of this inspection 17 subjects had completed the study and one subject had discontinued. Records reviewed during the inspection included informed consent documents, monitoring logs, delegation logs, enrollment logs, ethics committee correspondence and approvals, sponsor and monitor correspondence, investigator agreements, AE reports, IP accountability, and source documentation. Source documentation was specifically reviewed to verify efficacy and safety assessments.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

3. Dr. Tomasz Sarosiek, M.D. (Site 1010)

The site screened 47 subjects and randomized 20 subjects. A review of the screening and enrollment log found that of the 27 subjects that were screen failures 20 subjects failed screening due to HER-Negative status. At the time of this inspection, all 20 randomized subjects had completed the study through the end-of-study visit. Subjects are no longer being seen for this study. A record review was done for six enrolled subjects. The inspection included review of correspondences records, ethics committee approvals, AE/SAE reporting, delegation of authority, all subjects' Informed Consent Forms, study schedule adherence, training, investigator agreements, IP accountability, randomization, protocol deviations, and source study records for randomized subjects.

Subject binders included subjects' medical history records, inclusion/exclusion criteria components, dosing records, laboratory analysis results, HER (human epidermal growth factor receptor) status, pathology reports, adverse events documentation,

concomitant medications, physical exams, and vital signs. Source documents were compared to the line listings submitted by the Sponsor to the application. No discrepancies were found.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

4. Samsung Bioepis Co., Ltd.

The inspection of Samsung Bioepis focused on the control, oversight, and management of Study SB3-G31-BC. The inspection coverage included primary efficacy endpoint data verification and the firm's activities including, but not limited to, adherence to the study protocol, site records, selection of Clinical Investigators, monitoring, training, data management, IP accountability, AE reporting, sponsor's handling of noncompliant sites, and financial disclosures of investigators.

Study records in the electronic Trial Master File (eTMF) were reviewed from five clinical sites. Additional reviewed records included, but were not limited to, the Protocol and Amendments, Protocol signature pages, Investigator Brochure, Samsung Bioepis' SOPs, the clinical monitor (b) (4) SOPs, clinical monitor CVs and training records, monitoring reports, agreements between sponsor and CROs, corrective actions, safety reporting, IP accountability, DSMB meeting minutes and letters, final Clinical Study Report, and correspondence between sites, IRBs/ECs (including IRB/EC approval records), CRO, and sponsor, and other records in the eTMF.

The inspection revealed no significant deficiencies. Monitoring appeared adequate. There was adequate sponsor oversight over the conduct of the study to maintain GCP compliance and data integrity in the study database.

The data from this sponsor, associated with Study SB3-G31-BC, submitted to the Agency in support of BLA 761100, appear reliable.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
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Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. BLA #761100
DOP1/Division Director/Julia Beaver
DOP1/Clinical Team Leader/Laleh Amiri Kordestani
DOP1/Project Manager/Janice Kim
DOP1/Medical Officer/Tatiana Prowell
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
07/19/2018

SUSAN D THOMPSON
07/19/2018

KASSA AYALEW
07/19/2018

MEMORANDUM
NONPROPRIETARY NAME SUFFIX

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)

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Date of This Review:	July 10, 2018
Responsible OND Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761100
Product Name and Strength:	Ontruzant (trastuzumab-dttb) for Injection, 150 mg/vial
Product Type:	Single Ingredient Product
Applicant/Sponsor Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	October 20, 2017
OSE RCM #:	2017-2169
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffixes proposed by Samsung Bioepis for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761100.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

On October 20, 2017, Samsung Bioepis submitted a list of 5 suffixes, in their order of preference, to be used in the nonproprietary name of their product[a]. Table 1 presents a list of suffixes submitted by Samsung Bioepis:

Table 1. Suffixes submitted by Samsung Bioepis***

1.	(b) (4)
2.	dttb
3.	(b) (4)
4.	
5.	

We reviewed Samsung Bioepis's proposed suffixes in order of preference listed by Samsung Bioepis, along with the with the supporting information included in the submission, using the principles described in the applicable guidance.[b]

2.1 (b) (4)

Samsung Bioepis's first proposed suffix, (b) (4) does not align with the principles described in the final guidance that states "the proposed suffix should be four letters of which at least three are distinct". Thus, we find this suffix inconsistent with the principles described in our final guidance.

2.2 trastuzumab-dttb

Samsung Bioepis's second proposed suffix, -dttb, is comprised of three distinct letters ("d", "t", and "b"). Although the letters "t" and "b" are common to the core name **t**rastuzuma**b**, we do not find that the letters readily evoke the core name since the letters "tb" are positioned after the letters, "dt" in the suffix. Additionally, we could not identify a plausible risk related to the suffix evoking the core name trastuzumab.

We determined that the proposed suffix -dttb, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

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[a] Suffix Name Request. BLA 761100. Incheon (Republic of Korea): Samsung Bioepis Co., Ltd.; 2017 OCT 20. Available from: \\cdsesub1\evsprod\bla761100\0001\m1\us\118-prop-names\sb3-us-1-18-suffix-name-request.pdf

[b] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. Per an email correspondence dated July 6, 2018, OPDP did not identify any concerns that would render this proposed suffix unacceptable. DMEPA also communicated our findings to the Division of Oncology Products (DOP1) via e-mail on July 10, 2018.

4 CONCLUSION

We find Samsung Bioepis's proposed suffix -dttb acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to trastuzumab-dttb.

4.1 Recommendations for Samsung Bioepis

We find the nonproprietary name, trastuzumab-dttb, conditionally acceptable for your proposed product. Should your 351(k) BLA be approved during this review cycle, trastuzumab-dttb will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your suffix unacceptable upon our re-evaluation, we would inform you of our finding.

We also note that the first proposed suffix candidate is unacceptable for the following reasons:

(b) (4)

We find this suffix unacceptable as the proposed suffix is comprised of only two distinct letters. Thus, this suffix is inconsistent with the format described in FDA's final guidance on this topic, which recommends that suffixes be composed of at least three distinct letters.[b]

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/s/

TINGTING N GAO
07/10/2018

DANIELLE M HARRIS
07/12/2018

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)

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Date of This Review:	July 11, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761100
Product Name and Strength:	Ontruzant (trastuzumab-xxxx)[a] for Injection, 150 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	October 20, 2017 and February 9, 2018
OSE RCM #:	2017-2168
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

[a] Ontruzant has been developed as a proposed biosimilar to US-licensed Herceptin (Trastuzumab). Ontruzant, the proposed proprietary name is conditionally accepted until such time that the application is approved. Since the proper name for Ontruzant has not yet been determined, "trastuzumab-xxxx" is used throughout this review as the proper name for this product.

1 REASON FOR REVIEW

As part of the 351(k) BLA 761100 review for Ontruzant (trastuzumab-xxxx) for Injection[b], this review responds to a DOP1 consult requesting DMEPA to review the proposed Ontruzant 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 Ontruzant PI and find it acceptable from a medication error perspective.

3.2 CONTAINER LABEL AND CARTON LABELING

We reviewed the Ontruzant container label and carton labeling and determined that they may be improved to promote the safe use of the proposed product.

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

4 CONCLUSION & RECOMMENDATIONS

The proposed Ontruzant Prescribing Information is acceptable from a medication error perspective. The proposed Ontruzant container label and carton labeling may be improved to promote safe product use. We provide specific recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR SAMSUNG BIOEPIS

We recommend the following be implemented prior to approval of this BLA:

A. General recommendations for container label and carton labeling
    1. 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).

B. Container label
    1. Clarify the intention of repeating the LOT and EXP statements three times on the container label.

C. Carton labeling
    1. Relocate the "MERCK" logo away from the proprietary name to avoid misinterpretation of "MERCK" as the proprietary name for the product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ontruzant received on February 9, 2018 from Samsung Bioepis, and Herceptin retrieved from April 27, 2017 approved Herceptin Prescribing Information[c].

Table 2. Relevant Product Information for Herceptin and Ontruzant

Product Name	**Herceptin**	**Ontruzant**
Initial Approval Date	September 25, 1998	N/A
Active Ingredient	Trastuzumab	Trastuzumab-xxxx
Indication	treatment of HER2-overexpressing breast cancer treatment of 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	150 mg/vial
Dose and Frequency	**Adjuvant Treatment of HER2-Overexpressing Breast Cancer** Administer at either: • 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 IV infusion, then 6 mg/kg over 30-90 minutes intravenous infusion every three weeks for 52 weeks. **Metastatic HER2-Overexpressing Breast Cancer** • 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** 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.	

[c] 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 Ontruzant		
Product Name	**Herceptin**	**Ontruzant**
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 150 mg Single dose vial
Storage	Store in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.	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	A (b) (4) 15 mL glass vial, stoppered with a (b) (4) rubber stopper and sealed with an aluminum crimping cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

Although this is the first label and labeling review we conducted for BLA 761100, 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 Samsung Bioepis's proposed Ontruzant (trastuzumab-xxxx) for Injection product are consistent with our previous recommendations for other trastuzumab products. This search was conducted on February 2, 2018.

Trastuzumab products				
Application	**Applicant**	**Strength**	**Status**	**OSE Review**
BLA 103792 Herceptin (trastuzumab) for Injection	Genentech	150 mg/vial 420 mg/vial	420 mg/vial (originally labeled as 440 mg/vial): September 25, 1998 150 mg/vial: April 27, 2017	2013-2816[d] 2014-1298[e] 2016-2396[f] 2016-2396-1[g] 2017-463[h] 2017-463-1
BLA 761074 Ogivri (trastuzumab-dkst) for Injection	Mylan	420 mg/vial	Approved December 1, 2017	2016-2560[i]
BLA 761100 Ontruzant (trastuzumab-xxxx) for Injection	Samsung Bioepis	150 mg/vial	Subject of this review	2017-2168*

[d] 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.

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

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

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

[h] 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.

[i] 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 February 1, 2018, 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,[j] along with postmarket medication error data, we reviewed the following Ontruzant labels and labeling submitted by Samsung Bioepis.

- Container label received on October 20, 2017
- Carton labeling received on October 20, 2017
- Prescribing Information (Image not shown) received on February 9, 2018

G.2 Label and Labeling Images

Container label

(b) (4)

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

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

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/s/

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07/11/2018

CHI-MING TU
07/11/2018

U.S. FOOD & DRUG ADMINISTRATION

Consult Memorandum

Jacob R. Richards -S
2018.02.14 09:56:15
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Date:	February 14, 2018
To:	Janice Kim, RPM and Tatiana Prowell, MO, CDER/OND/OHOP/DOPI
From:	Jacob Richards, Scientific Reviewer, OIR/DMGP/MPCB
Through:	Eunice Lee, Branch Chief, OIR/DMPP/MPCB; Yun-Fu Hu, Deputy Division Director and Reena Philip, Division Director, OIR/DMGP
ICC Number:	1800107
Subject:	BLA 761100 – Revised Labeling for ONTRUZANT- Samsung
Biomarker(s):	HER2

I. BACKGROUND and PURPOSE

A consult request was received from CDER on January 31, 2018 requesting CDRH to comment on the product label for ONTRUZANT (reviewed under BLA 761100), under sections 1.1, 1.2, 1.3, 2, and 14 regarding the statement for the companion diagnostic. There was no requirement for a companion diagnostic for ONTRUZANT, since it is a biosimilar to trastuzumab (for which there are FDA-approved companion diagnostic tests). CDER is seeking CDRH input on whether the same language regarding companion diagnostics for "a trastuzumab product" that was used for recently approved BLA761074 for OGIVRI would be acceptable for ONTRUZANT. Additionally, CDER is seeking input on whether the applicant's justification of the use of the companion diagnostics for trastuzumab for the Samsung product ONTRUZANT, based on CDER's information requests sent on January 19, 2018 and February 5, 2018, is acceptable.

II. CDRH RESPONSE TO CDER QUESTIONS

In the sponsor's response to CDER's information request received on January 26, 2018, Samsung concurred that FDA-approved companion diagnostics are important for selecting patients who would benefit from ONTRUZANT. They further noted that given that ONTRUZANT is highly similar to Herceptin based on physico-chemical and biological characterization, nonclinical, pharmacokinetic, safety, efficacy, and immunogenicity data with no clinically meaningful differences with Herceptin, FDA-approved companion diagnostics for Herceptin are expected to serve the same purpose for ONTRUZANT. The sponsor provided updated labeling in response to CDER's second information request on February 9, 2018. Additionally, in both Samsung's comparative and supportive clinical studies, an FDA-approved companion diagnostic for trastuzumab was required to confirm HER2-positivity.

We believe Samsung's responses are adequate. Further, based on the sponsor's justification and the proposed therapeutic labeling in section 14 referencing the original trastuzumab clinical studies, we agree that the same language regarding "an FDA-approved companion diagnostic for a trastuzumab product", which is used in the OGIVRI product label, would be acceptable for the ONTRUZANT label.

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/s/

JACOB R RICHARDS
02/14/2018