

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125427Orig1s000

MICROBIOLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 12 February 2013
To: Administrative File, STN 125427/0
From: Patricia F. Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject: Team Leader Review Memo: Microbiology Product Quality Assessment of the BLA
US License: 1048
Applicant: Genentech, Inc.
Facilities: Drug substance manufacturer - (b) (4) FEI
(b) (4)
Drug Product manufacturer - (b) (4) (FEI)
(b) (4)
Product: KADCYLA™ (ado-trastuzumab emtansine)
Dosage: Lyophilized cake (100 mg/vial and 160 mg/vial) for reconstitution with sterile WFI to a final concentration of 20 mg/mL (5.0 mL and 8.0 mL) to be delivered by infusion
Indication: Treatment of patients with HER2-positive (b) (4) metastatic breast cancer which have received prior treatment with trastuzumab and a taxane
Due date: 26 February 2013

Recommendation for Approvability from a CMC Product Quality Microbiology Perspective:

The drug substance and the drug product quality sections of the BLA were reviewed by DGMPA/BMAB product quality microbiology reviewers Bo Chi, Ph.D. (drug substance) and Reyes Candau-Chacon, Ph.D. (drug product). The BLA sections were assessed from a microbial control, sterility assurance and microbiology product quality perspective. The BLA, as amended, is recommended for approval from a microbiology product quality perspective. Six post-marketing commitments (PMCs) should be communicated to the sponsor. The PMCs are as follows:

1. Conduct endotoxin spiking and recovery studies (b) (4)
(b) (4)
Submit the final report as a Changes Being Effected in 30 days Supplement (CBE-30). The final report should be submitted by 05/13.
2. Transfer the methodology for validated dye ingress method developed by Genentech to (b) (4).
Conduct a study to confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and provide a final report in the 2014 annual report.

3. Conduct a study to assess the risk of endotoxin masking (b) (4) using endotoxin spiked ado-trastuzumab emtansine drug product (b) (4). Submit a final report that includes updated specifications as a Prior Approval Supplement. 29-Mar-2013 as a PAS. The final report should be submitted by 03/13.
4. If endotoxin masking is observed in the drug product (b) (4), develop an alternative method to quantitate endotoxin (b) (4) using routine production conditions. Any change in the analytical methods should be approved by the Agency before implementation. Submit protocol to the Agency by 30-June-2013 as a PAS.
5. Dedicate (b) (4) for ado-trastuzumab emtansine drug product manufacture and submit results from sterilization validation and 3 media fill simulations to the Agency by 30-June-2013 as a CBE-0.
6. Conduct cleaning verification (b) (4) until (b) (4) is implemented and report the updated (b) (4) procedures to the Agency in the 2014 Annual Report.

CGMP Assessment of Establishments:

All sites listed in the BLA were submitted for a CGMP assessment through a TB-EER request (CDER-TB-EER@fda.hhs.gov). The final TB-EER report should be submitted to DARRTS 15-30 days prior to the action date by NDMAB (New Drug Manufacturing Assessment Branch). This TB-EER report will provide the final CGMP assessment of the sites listed in the BLA. As of the date of this memo, a final TB-EER is pending.

Three establishments were inspected in support of the approval of this BLA:



The final decision on the CGMP status of these establishments is pending by NDMAB (through a TB-EER in DARRTS).

Background Assessment Summary

The drug substance and the drug product quality sections of the BLA were reviewed by DGMPA/BMAB reviewers Bo Chi, Ph.D. (drug substance) and Reyes Candau-Chacon, Ph.D. (drug product). The BLA sections were assessed from a microbial control, sterility assurance and microbiology product quality perspective. The BLA, as amended, is recommended for approval from a microbiology product quality perspective. Deficiencies encountered during the review involved the sterilization of sterile product components, the endotoxin test validity due to potential

endotoxin masking effects, the container closure integrity test conducted at the contract manufacturer (b) (4)

The deficiencies were resolved by the submission of additional data and information from completed studies and through PMCs. (b) (4)

concerns associated with market launch lots manufactured (b) (4) were mitigated with the submission of cleaning verification data (b) (4)

on February 11, 2013. The total (b) (4) from rinse and swab samples from each of three runs (b) (4) were below the cleaning acceptance criteria (b) (4). These criteria are based on acceptable daily exposure (ADE) (b) (4)

(b) (4) will continue to conduct cleaning verification (b) (4)

of ado-trastuzumab emtansine (PMC 5 below).

Six post-marketing commitments (PMCs) should be communicated to the sponsor. The PMCs and the rationale are as follows:

1. Conduct endotoxin spiking and recovery studies (b) (4)

Submit the final report as a Changes Being Effected in 30 days Supplement (CBE-30). The final report should be submitted by 05/13.

Rational: Previous study results indicated (b) (4)

The validity of the drug substance in-process endotoxin test will be evaluated (b) (4)

2. Transfer the methodology for validated dye ingress method developed by Genentech to (b) (4). Conduct a study to confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and provide a final report in the 2014 annual report.

Rational: The current dye ingress container closure integrity test used at (b) (4) uses different parameters from those used in the validated method developed by Genentech. However, vials with known breach sizes were tested using both methods and the number of positive control vials was comparable; therefore, the risk of not detecting breached vials with the non-validated method is deemed low.

3. Conduct a study to assess the risk of endotoxin masking (b) (4) using endotoxin spiked ado-trastuzumab emtansine drug product (b) (4)

Submit a final report that includes updated specifications as a Prior Approval Supplement. 29-Mar-2013 as a PAS. The final report should be submitted by 03/13.

Rational: The release test for endotoxin in the finished product may be inadequate. The study will determine the adequacy of the test. Previous studies conducted by the Sponsor suggest endotoxin masking of T-DMI (b) (4). However, the impact of endotoxin masking in (b) (4) samples is unclear. The sponsor will study endotoxin masking in (b) (4) samples to assess the validity of the standard LAL test in finished drug product. Until those results are available, endotoxin will be tested in the sterile bulk (b) (4)

Since there is no endotoxin masking (b) (4) under (b) (4) conditions, the risk for the introduction of endotoxin (b) (4)

in the final vials is deemed low. (b) (4)

4. If endotoxin masking is observed in the drug product (b)(4), develop an alternative method to quantitate endotoxin in the finished ado-trastuzumab emtansine drug product (b)(4) using routine production conditions. Any change in the analytical methods should be approved by the Agency before implementation. Submit protocol to the Agency by 30-June-2013 as a PAS.

Rational: Previous studies conducted by the Sponsor suggest endotoxin masking of T-DM1 (b)(4) and the Sponsor will study endotoxin masking in (b)(4) samples. If those studies demonstrate that the standard LAL test for endotoxin determination in the finished drug product is not adequate, the sponsor will develop an alternative endotoxin release method for finished product. Until those results are available, endotoxin will be tested in the sterile bulk. Since there is no endotoxin masking (b)(4), the risk for false endotoxin negatives in the finished product is deemed low.

5. Dedicate the (b)(4) for ado-trastuzumab emtansine drug product manufacture and submit results from sterilization validation and 3 media fill simulations to the Agency by 30-June-2013 as a CBE-0.

Rational: T-DM1 (b)(4) sterilization validation and media fill simulations must be conducted (b)(4)
The sterilization process validation data and media fill studies will provide sterility assurance for the sterile hold of the bulk drug product.

6. Conduct cleaning verification after (b)(4) until (b)(4) is implemented and report the updated (b)(4) procedures to the Agency in the 2014 Annual Report.

Rational: T-DM1 (b)(4) cleaning verification (b)(4) will be conducted to ensure that (b)(4) are below the cleaning acceptance criteria. (b)(4) will ensure that (b)(4) are deemed safe.

Additional information on the establishments:

Ado-trastuzumab emtasine, an antibody-drug conjugated (ADC), is manufactured at several Genentech and contract facilities listed in the BLA. The main manufacturing establishments are as follows:

- Trastuzumab intermediate:
 - Genentech in Vacaville, CA (FEI 3002902534) –inspection waived
 - Roche Singapore Technical Operations PTe. Ltd, Singapore 637394 (FEI 3007164129) – inspection waived
- DM 1 Intermediate
 - (b)(4)

- [Redacted] (b) (4)
- Drug substance
 - [Redacted] (b) (4)
- Drug product
 - [Redacted] (b) (4)

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/s/

PATRICIA F HUGHES TROOST
02/13/2013



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 12 February 2013
To: Administrative File, STN 125427/0
From: Reyes Candau-Chacon, Ph.D., Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA)
US License: 1048
Applicant: Genentech, Inc.
Facilities: [REDACTED] (b) (4)
(FEI # [REDACTED] (b) (4))
Product: KADCYLA™ (ado-trastuzumab emtansine)
Dosage: Lyophilized cake (100 mg/vial and 160 mg/vial) for reconstitution with sterile WFI to a final concentration of 20 mg/mL (5.0 mL and 8.0 mL) to be delivered by infusion
Indication: Treatment of patients with HER2-positive [REDACTED] (b) (4) metastatic breast cancer which have received prior treatment with trastuzumab and a taxane
Due date: 26 February 2013

The purpose of this addendum is to review cleaning verification results of the [REDACTED] (b) (4) drug product contract manufacturer for T-DM1. As per T-con held between DSM and BMAB on January 24, 2013, a cleaning verification report after manufacture of three [REDACTED] (b) (4) consecutive batches was submitted to the Agency. The report includes [REDACTED] (b) (4) using swab and rinse samples.

Genentech Response in Amendment 0098

Swab samples were taken [REDACTED] (b) (4)

The cleaning verification results show total [REDACTED] (b) (4) from rinse and swab samples below the cleaning acceptance criteria [REDACTED] (b) (4) based on acceptance daily exposure (ADE) [REDACTED] (b) (4) recommended by the Agency. Therefore, the results support the adequacy and consistency of the T-DM1 [REDACTED] (b) (4) cleaning process.

Reviewer comments

The ^{(b) (4)} cleaning verification results after manufacture of three consecutive batches ^{(b) (4)} support the adequacy and state of control of the ^{(b) (4)} cleaning process. Based on those results, the T-DM1 lots manufactured ^{(b) (4)} are deemed safe in that regard to be release for clinical or market launch.

Satisfactory

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/s/

REYES CANDAU-CHACON
02/12/2013

PATRICIA F HUGHES TROOST
02/12/2013



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 1/15/2013
To: Administrative File, STN 125427/0
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Applications (BLA)
Applicant: Genentech, Inc.
US License: 1048
Facility: (b) (4)
FEI: (b) (4)
Product: KADCYLA™ (ado-trastuzumab emtansine)
Dosage: 100 mg and 160 mg vials (20 mg/ml), Sterile lyophilized single use vial, intravenous infusion
Indication: Single agent for treatment of patients with HER2-positive metastatic breast cancer
PDUFA date: 2/26/2013

Recommendation: The drug substance part of this application is recommended for approval from product quality microbiology perspective with the following post-market commitment:

Conduct endotoxin spiking and recovery studies (b) (4)
Submit the information and study results in a CBE-30 by May 31, 2013.

Review Summary

Genentech has submitted this Biologics License Application (BLA) for trastuzumab emtansine, an antibody-drug conjugate (ADC) for treatment of patients with HER2-positive metastatic breast cancer and who have relapsed from prior HER2-directed treatments. The drug substance (DS) is manufactured (b) (4). The drug product (DP) is manufactured (b) (4). The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of trastuzumab emtansine drug substance from microbiology perspective. The BLA refers to the approved Herceptin BLA STN103792 for the manufacturing process of the trastuzumab intermediate. Therefore, the manufacturing process of the trastuzumab intermediate was not reviewed.

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

Trastuzumab emtansine consists of the antibody trastuzumab (humanized anti-HER2 IgG1) conjugated via a thioether bond to the cytotoxic microtubule-inhibitory maytansinoid, DM1. The DM1 is linked to the lysine residues on the antibody via trans-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC). Trastuzumab emtansine contains an average of 3.5 DM1 molecules per antibody, as determined by UV spectroscopy, and is made up of a mixture of forms containing from 0 to 8 linked DM1 molecules per antibody.

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

Trastuzumab intermediate manufacturer, lot release and stability testing

Genentech

1000 New Horizons Way

Vacaville, CA 94080

FEI: 3002902534

Roche Singapore Technical Operations PTe. Ltd.

Singapore 637394

FEI: 3007164129

Reviewer comment: Roche Diagnostics GmbH at Penzberg, Germany was initially submitted in the original BLA as a trastuzumab intermediate manufacturer. It was later removed from the BLA by the sponsor.

Drug substance manufacturing, batch release testing, and stability testing

(b) (4)
[Redacted]
FEI: [Redacted] (b) (4)

Description of Manufacturing Process and Process Controls (3.2.S.2.2)

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cGMP Status:

A pre-license inspection was conducted [REDACTED] (b) (4) A four-item Form FDA 483 was issued. The inspection was classified as VAI. The pre-approval inspections at the trastuzumab manufacturing sites have been waived (see the inspectional waiver memos in DARRTS). See TB-EER for GMP status of the relevant facilities.

Conclusion

I. The drug substance section of the BLA is recommended for approval from a product quality microbiology perspective with the following post-market commitment:

Conduct endotoxin spiking and recovery studies [REDACTED] (b) (4)

Submit the information and study results in a CBE-30 by May 31, 2013.

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the DMA reviewer.

III. A pre-license inspection was conducted [REDACTED] (b) (4) [REDACTED] A four-item Form FDA 483 was issued. The inspection was classified as VAI. The pre-approval inspections at the trastuzumab manufacturing sites have been waived (see the inspectional waiver memos in DARRTS). See TB-EER for GMP status of the relevant facilities.

Cc: WO51: Chi
WO51: Hughes
WO22: Skarupa

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/s/

BO CHI
01/28/2013

PATRICIA F HUGHES TROOST
01/28/2013