CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s000

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: **6/5/2012**
To: Administrative File, **STN 125409/0**
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Addendum to review memo for New Biologic License Applications (BLA) STN125409/0 dated 5/22/2012
Applicant: Genentech, Inc.
US License: **1048**
Facility: Genentech
1000 New Horizons Way
Vacaville, CA 95688-9431
FEI: 3002902534
Product: Perjeta™ (pertuzumab)
Dosage: 420 mg/20 mL, liquid single use vial, intravenous injection
Indication: For the treatment of patients with 1st Line HER2-positive metastatic breast cancer
PDUFA date: June 8, 2012

Recommendation: The drug substance part of this application is recommended for approval from product quality microbiology perspective with two post-market requirements (PMRs, see below) and one post-market commitment (PMC, see below).

The BLA is not recommended for approval to manufacture pertuzumab drug substance in the Genentech Vacaville, CA facility under the U.S. License 1048. This is the recommendation from the DGMPA/OMPQ documented in the final TB-EER for BLA 125409.

PMRs

1. To evaluate the potential for serious risk of contamination, revalidate the hold time for non-sterile cell culture media with a (b) (4) acceptance criterion that demonstrates microbial control. Test three different lots of raw materials in the re-validation runs.

   Final Protocol Submission: 04/2013
   Study Completion: 08/2013
   Final Report Submission: 12/2013

2. To evaluate the serious risk of resistant microorganisms and contamination, conduct a comprehensive risk assessment regarding the microbial control of the cell culture process

and generate an action plan based on the assessment. The risk assessment will consider the feasibility of (b) (4), the screening of raw materials for (b) (4) bioburden and endotoxin, the (b) (4) of the non-sterile media hold time and temperature (b) (4) and the expanded use of (b) (4).

Final Protocol Submission: 09/2012
Final Report Submission: 03/2013

PMC:

Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use 10 mL sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b) (4). Submit the final study report as a Changes Being Effected-0 (CBE-0).

Final Protocol Submission: 06/2012
Study Completion: 07/2012
Final Report Submission: 12/2012

This review amends the drug substance review memo for Genentech's BLA STN125409/0 by Bo Chi dated 5/22/12 to update the information on post-market commitments (PMCs)/post-market requirements (PMRs). Due to the potential for serious risk of resistant microorganisms and contamination, it is necessary to convert two of the three PMCs to PMRs (see above).

Cc: WO51: Chi
WO51: Hughes
WO22: Tilley

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/s/

BO CHI
06/06/2012

PATRICIA F HUGHES TROOST
06/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: **5/22/2012**
To: Administrative File, **STN 125409/0**
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: Genentech
1000 New Horizons Way
Vacaville, CA 95688-9431
FEI: 3002902534
Product: Perjeta™ (pertuzumab)
Dosage: 420 mg/20 mL, liquid single use vial, intravenous injection
Indication: For the treatment of patients with 1st Line HER2-positive metastatic breast cancer
PDUFA date: June 8, 2012

Recommendation: The drug substance part of this application is recommended for approval from product quality microbiology perspective with three post-market commitments (PMCs, see below).

The BLA is not recommended for approval to manufacture pertuzumab drug substance in the Genentech Vacaville, CA facility under the U.S. License 1048. This is the recommendation from the DGMPA/OMPQ documented in the final TB-EER for BLA 125409.

PMCs

1. Revalidate the hold time for non-sterile cell culture media with a [redacted] (b) (4) acceptance criterion that demonstrates microbial control. In addition, test three different lots of raw materials in the re-validation runs. The information and results of the revalidation study will be submitted in a CBE-30 by December 31, 2013.

2. Conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. The risk assessment will consider the feasibility of [redacted] (b) (4), the screening of raw materials for [redacted] (b) (4) bioburden and endotoxin, the [redacted] (b) (4) of the non-sterile media hold time and temperature [redacted] (b) (4) and the expanded use of [redacted] (b) (4). The risk assessment summary and action plan will be submitted in a CBE-30 by March 31, 2013.

3. Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use10 mL sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b) (4) . The summary data will be provided in a CBE0 by December 31, 2012.

Review Summary

Genentech has submitted this Biologics License Application (BLA) for pertuzumab, a recombinant monoclonal antibody that binds to the human epidermal growth factor receptor 2 (HER2) for the treatment of patients with 1st Line HER2-positive metastatic breast cancer. The drug substance (DS) is manufactured at Genentech, Vacaville, CA. The drug product (DP) is manufactured at Roche Diagnostics GmbH, Mannheim, Germany. The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of pertuzumab drug substance from microbiology perspective.

(b) (4)

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Environmental Assessment:

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.15(d) and 25.31(c) was provided by the firm. Genentech is not aware of any extraordinary circumstances that exist with the use of this product that would warrant the preparation of an environmental assessment.

cGMP Status:

A pre-license inspection was conducted at the Genentech Vacaville facility on 3/20-28/12. DGMPA/OMPQ recommended withhold the approval of the BLA based on the recent cell culture failures in the Pertuzumab manufacturing campaign and the inability of consistently manufacturing at the Vacaville facility.

Conclusion

I. The drug substance section of the BLA is recommended for approval from a product quality microbiology perspective with three post-market commitments (see below).

The BLA is not recommended for approval to manufacture pertuzumab drug substance in the Genentech Vacaville, CA facility under the U.S. License 1048. This is the recommendation from the DGMPA/OMPQ documented in the final TB-EER for BLA 125409.

PMCs

1. Revalidate the hold time for non-sterile cell culture media with a (b) (4) acceptance criterion that demonstrates microbial control. In addition, test three different lots of raw materials in the re-validation runs. The information and results of the revalidation study will be submitted in a CBE-30 by December 31, 2013.

2. Conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. The risk assessment will consider the feasibility of (b) (4), the screening of raw materials for (b) (4) bioburden and endotoxin, the (b) (4) of the non-sterile media hold time and temperature (b) (4) and the expanded use of (b) (4). The risk assessment summary and action plan will be submitted in a CBE-30 by March 31, 2013.

3. Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use10 mL sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b) (4) The summary data will be provided in a CBE0 by December 31, 2012.

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

III. A pre-license inspection was conducted at the Vacaville facility on 3/20-28/12. DGMPA/OMPQ recommended withhold the approval of the BLA based on the recent cell culture failures in the Pertuzumab manufacturing campaign and the inability of consistently manufacturing at the Vacaville facility.

Cc: WO51: Chi
WO51: Hughes
WO22: Tilley

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/s/

BO CHI
05/24/2012

PATRICIA F HUGHES TROOST
05/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: 14 May 2012

To: Administrative File, STN 125409

From: Colleen Thomas, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB

Endorsed: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB

Subject: Original BLA for pertuzumab

US License: 1048

Applicant: Genentech, Inc.

Facility: Roche Diagnostics GmbH, Sandhoferstrasse 116, 68305 Mannheim, Germany (FEI 3002806559)

Product: pertuzumab (Perjeta)

Indication: Indicated in combination with Herceptin (trastuzumab) and docetaxel for patients with HER-2 positive metastatic (b) (4) breast cancer, who have not received previous treatment (b) (4)

Dosage: Sterile, preservative-free, liquid for intravenous infusion. Supplied in single-use 20 ml vials (420 mg in 14 ml). The dosage is 840 mg initially and 420 mg every three weeks thereafter. The infusion is prepared by mixing the drug product with 250 ml of 0.9% sodium chloride.

Due date: 8 June 2012

Recommendation for approvability: The drug product portion of the BLA was reviewed from a product quality microbiology perspective and is recommended for approval.

Summary

Genentech, Inc. submitted BLA 125409 to license pertuzumab and the associated drug substance and drug product manufacturing processes. Pertuzumab is a recombinant, humanized monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) and is indicated for

treatment of patients with HER2-positive metastatic breast cancer. The drug product is supplied as a sterile, preservative-free liquid for intravenous infusion.

This review is a product quality microbiology review for the drug product. The drug substance is covered in a separate product quality microbiology review. Product quality aspects other than microbial control and sterility assurance are reviewed by OBP. The table below lists the amendments included in this review.

Amendments Reviewed for Drug Product Quality Microbiology

Information request (IR) date	Question numbers	Amendment number (sequence)	Amendment date
2-Mar-2012	36-43	0014	15-Mar-2012
12-Apr-2012	all	0030	26-Apr-2012
26-Apr-2012	1, 2	0035	4-May-2012
8-May-2012	all	0040	11-May-2012
3-May-2012	all	0041	11-May-2012

(b) (4)

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3.2.R Regional Information

(b) (4)

Environmental Assessment

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(c) was provided by the firm on the grounds the substances associated with this submission occurs naturally in the environment and the actions associated with this submission do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Conclusion

I. The BLA was reviewed from a product quality microbiology perspective and is recommended for approval.

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. A pre-license inspection of the Roche facility in Mannheim, Germany was conducted on 18-26 April, 2012 by ORA. There were four inspectional observations listed on Form FDA 483. Please refer to the EIR.

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/s/

COLLEEN THOMAS
05/22/2012

PATRICIA F HUGHES TROOST
05/22/2012