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RESEARCH**

*APPLICATION NUMBER:*

**125409Orig1s000**

**CHEMISTRY REVIEW(S)**

# Review Cover Sheet

**BLA STN 125409**

**Pertuzumab**

**Genentech, Inc**

**Kathryn King (Traditional Elements Reviewer)  
Laurie Graham (Quality by Design Reviewer)**

**Division of Monoclonal Antibodies; HFD-123**

# Product Quality Review Data Sheet

1. **BLA#** STN 125409
2. **REVIEW #:** 1
3. **REVIEW DATE:** May 31, 2012
4. **REVIEWERS:** Laurie Graham, M.S. (Quality by Design, QbD, Reviewer)  
 Kathryn King, Ph.D. (Traditional Elements Reviewer)  
 Barbara Rellahan, M.S., Ph.D.  
 Product Quality Team Leader (QbD Team Leader)  
 Wendy Weinberg, Ph.D.  
 Chief, Laboratory of Molecular Oncology (Team Leader)

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

| <u>Communication/Document</u> | <u>Date</u>       |
|-------------------------------|-------------------|
| CMC Pre-BLA Meeting           | August 12, 2011   |
| Filing Review Memo            | February 17, 2012 |
| Information Request Letter #1 | March 2, 2012     |
| Information Request Letter #2 | March 22, 2012    |
| Information Request Letter #3 | April 26, 2012    |
| Teleconference #1             | March 30, 2012    |
| Teleconference #2             | April 2, 2012     |
| Teleconference #3             | April 4, 2012     |
| Teleconference #4             | April 12, 2012    |
| Teleconference #5             | April 24, 2012    |
| Teleconference #6             | April 25, 2012    |
| Teleconference #7             | May 2, 2012       |
| Teleconference #8             | May 8, 2012       |
| Teleconference #9             | May 9, 2012       |
| Teleconference #10            | May 16, 2012      |

6. **SUBMISSION(S) BEING REVIEWED:**

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|-------------------------------|----------------------|
| STN 125409/0                  | 12/8/2011            |
| STN 125409/20                 | 3/28/2012            |
| STN 125409/21                 | 4/2/2012             |
| STN 125409/23                 | 4/9/2012             |
| STN 125409/24                 | 4/9/2012             |
| STN 125409/26                 | 4/12/2012            |
| STN 125409/27                 | 4/16/2012            |
| STN 125409/32                 | 5/1/2012             |
| STN 125409/35                 | 5/4/2012             |
| STN 125409/36                 | 5/8/2012             |
| STN 125409/39                 | 5/10/2012            |
| STN 125409/42                 | 5/11/2012            |

|               |           |
|---------------|-----------|
| STN 125409/46 | 5/16/2012 |
| STN 125409/47 | 5/16/2012 |
| STN 125409/50 | 5/17/2012 |
| STN 125409/51 | 5/17/2012 |
| STN 125409/52 | 5/18/2012 |
| STN 125409/53 | 5/21/2012 |
| STN 125409/55 | 5/22/2012 |
| STN 125409/56 | 5/23/2012 |

**7. NAME & ADDRESS OF APPLICANT:**

**Name:** Genentech, Inc  
**Address:** 1 DNA Way  
 South San Francisco, CA 94080-4990  
 FDA registration number: 2917293  
**Representative:** Michelle H. Rohrer, Vice President, Regulatory Affairs  
**Telephone:** 650-225-1558

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Pertuzumab
- b) Non-Proprietary/USAN: Pertuzumab
- c) Code name: rhuMab 2C4
- d) Common name: Perjeta
- e) Drug Review Status: Original Application
- f) Chemical Type:
- g) CAS index/registry no.: 380610-27-5
- h) Internal systematic name: MAB Humanized (IgG1k) ANTI P04626 (ERBB2\_HUMAN)

**9. PHARMACOL. CATEGORY:** Humanized IgG1 kappa immunoglobulin molecule.

**10. DOSAGE FORM:** Sterile parenteral solution.

**11. STRENGTH/POTENCY:**

- a) The concentration of pertuzumab Drug Product is 30mg/ml
- b) Potency is defined as the inhibition of proliferation of HER2 expressing MDA-MD-175 breast cancer cells
- c) The potency specification is: (b)(4) determined relative to reference standard
- d) Dating period for vialled drug product is 24 months at 2-8°C
- e) Pertuzumab is filled into 20 mL glass vials containing (b)(4) 14.0 ml (420 mg)

**12. ROUTE OF ADMINISTRATION:** intravenous infusion

**13. ACID (Animal Component Information Database)**

Refer to BLA 125409, section 3.2.S.2.3.1 "Control of Source and Starting Materials of Biological Origin" of this review for animal/human derived component information.

**14. RELATED/SUPPORTING DOCUMENTS:**

| DMF # | HOLDER | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS |
|-------|--------|-----------------|-------------------|---------------------|-----------------------|----------|
|       |        |                 |                   |                     |                       |          |

|         |         |         |   |     |  |  |
|---------|---------|---------|---|-----|--|--|
| (b) (4) | (b) (4) | (b) (4) | 4 | N/A |  |  |
| (b) (4) | (b) (4) | (b) (4) | 4 | N/A |  |  |

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

15. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

| CONSULTS/ CMC RELATED REVIEWS                   | RECOMMENDATION   | DATE    | REVIEWER         |
|---|--|---------|------------------|
| Drug Substance Establishment Status             | The 483 items cited on this inspection could generally be classified as VAI (voluntarily action indicated), but the deviation and follow up data supplied from the firm related to their inability to successfully thaw and grow cultures from their working cell bank lead Office of Compliance to concur with the recommendation to withhold on this application by Division of Monoclonal Antibodies. | 5/18/12 | Shawn Gould      |
| Drug Product Establishment Status               | A pre-license inspection of the Roche facility in Mannheim, Germany was conducted on April 18-26, 2012 by ORA. See EIR.  | 5/14/12 | Colleen Thomas   |
| Environmental Assessment                        | Approval   | 5/31/12 | Kathryn King     |
| BMAB- memo for Drug Substance facilities review | Drug substance is recommended for approval from product quality microbiology perspective.<br><br>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.   | 5/22/12 | Bo Chi           |
| BMAB – memo for Drug Product facilities review  | Approval   | 5/14/12 | Colleen Thomas   |
| DDMAC Carton and vial labeling                  | Approval   | 6/1/12  | Marybeth Toscano |
| OBP Carton and vial labeling                    | Approval   | 5/31/12 | Kimberly Rains   |
| DMETS/DDMAC – trade name review                 | Approval   | 5/7/12  | Carol A Holquist |

|                                 |   |         |                   |
|---------------------------------|---|---------|-------------------|
| Pharmacology/Toxicology Consult | The information publically available for the raw materials provided in Table 3.2.S.3.2-28 support the ADI values provided by the applicant. There are no pharmacology/toxicology concerns at this time. | 2/20/12 | Kimberly Ringgold |
| Biostatistics Consult           | The consult identified multiple issues regarding the assessment of equivalence between the small scale models and the full scale process.   | 3/16/12 | Youngsook Jeon    |

(1) DMPQ review date states VAI has not been changed since EIR

### 16. Inspectional Activities

A pre-approval inspection (PAI) for pertuzumab drug substance manufacture was performed at the Vacaville (VV), CA facility from March 20 to March 28, 2012 by BMT reviewer Bo Chi (lead), BMT trainee Qing Zhou, product reviewers Kathryn King and Laurie Graham and an inspector from the San Francisco District, Lance DeSouza. VV is responsible for the manufacture of pertuzumab drug substance and for DS QC testing. A form 483 was issued at the end of this inspection. Observations included: 1) The environment of (b)(4) facility where pertuzumab is manufactured is not maintained in a clean and sanitary condition; 2) There is a lack of assurance that water used in (b)(4) is suitable for its intended use; 3) Equipment cleaning validation studies are inadequate; 4) There is a lack of systematic oversight of the DCS (distributed control system) used to monitor and control process performance; 5) Quality oversight of documentation is inadequate; 6) There is inadequate control of raw materials. In addition, while inspecting the facility, we discovered that the Sponsor was experiencing serious issues with the thaw and subsequent propagation of cells from WCB (b)(4) used to manufacture pertuzumab. At the time of inspection, the root cause investigation was ongoing and no root cause had been identified, although data suggested instability of WCB (b)(4) WCB (b)(4) is under the control of the (b)(4) cell banking group. Based on these facts, the decision was taken to bring this back to the division as a review issue. Regarding the classification, the following statement was received from Shawn Gould, Compliance Officer by e-mail on May 18, 2012: “The Office of Compliance has completed its review of the materials from the pre-license inspection for Genentech's BLA STN125409/0 (pertuzumab). The 483 items cited on this inspection could generally be classified as VAI (voluntarily action indicated), but the deviation and follow up data supplied from the firm related to their inability to successfully thaw and grow cultures from their working cell bank lead us to concur with the **recommendation to withhold** on this application by Division of Monoclonal Antibodies.”

Roche Diagnostics GmbH, Mannheim, Germany is the site of drug product manufacture (b)(4) It was inspected by ORA from April 18 to April 26, 2012. A form 483 containing four observations was issued (refer to EIR). All other facilities listed in the BLA (b)(4) were not inspected. Inspections were not conducted as the activities in these sites are either low risk and/or these sites are in compliance as per 21 CFR 210, 211 and 600.

### 17. Recommendations on Approvability:

#### Recommendation on Traditional Elements:

During inspection of the drug substance manufacturing site and in subsequent discussions of data submitted with respect to failures of cell growth, it became apparent that the drug substance manufacturing process is not currently in a state of control (see section 3.2.S.2.3.3 of this review “Cell Culture Investigation”). Following discussions with the Agency, the Sponsor has initiated three concurrent plans to resolve the cell growth issues associated with manufacturing: 1) manufacturing from the MCB; 2) developing a new WCB and manufacturing from this new WCB; and 3) manufacturing using a modified process from WCB (b)(4) Any one of these

approaches might be sufficient in the short term to support a validated process for the manufacture of pertuzumab drug substance, however currently there is not a validated process. Process validation is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)) and FDA regulations require that process validation procedures be established and followed (§ 211.100) before a batch can be distributed (§§ 211.22 and 211.165). **As the Sponsor does not have a validated process, from a CMC perspective, it is not possible to recommend approval of this license at this time.** Based on information provided by the Sponsor, data from manufacture of 3 batches of drug substance from the MCB are anticipated to be available in early August. If along with associated process validation study data these are acceptable, the process could be validated for manufacture from the MCB. This appears to be the fastest mechanism available. Therefore, it is recommended that FDA extend the review clock for 3 months via a major amendment mechanism based on a major amendment received in May to allow this exercise to be completed and the data to be reviewed by the Agency. If the review clock cannot be extended, a Complete Response letter is recommended, as data have not been provided that support the Sponsor's ability to consistently manufacture pertuzumab by a validated process.

Unfortunately, the applicant has refused to make this product available through an expanded access program to patients prior to licensure, which could have been a mechanism whereby seriously ill patients could obtain pertuzumab whilst the manufacturing issues were being addressed. Out of concern for the seriously ill patients who stand to benefit from this therapy for an unmet medical need, the clinical division has indicated they intend to approve this product within a time frame consistent with the PDUFA deadline and to resolve outstanding manufacturing issues post-licensure. A meeting was held with the Center Director on May 18, 2012, who agreed that because the conformance lots that were manufactured in 2010 prior to the cell culture failures allow for a <sup>(b) (4)</sup> supply of pertuzumab (as estimated by the Sponsor) of acceptable quality, and because this product is for a life-threatening condition and there is an unmet medical need for this product, the CMC concerns regarding validation of the drug substance manufacturing process would be handled as Post Marketing Requirements. Therefore, DMA has participated in drafting of PMRs as the only remaining mechanism to mitigate risks to product quality from a process which lacks adequate validation. A list of these PMRs is provided below under III, "List of Deficiencies to be communicated".



(b) (4)

<sup>(b) (4)</sup>, there were 2 post marketing requirements (PMRs) and 1 post marketing commitment (PMC). These are PMRs #6 and #7 and PMC #1 under section III below, "List of Deficiencies to be communicated".



(b) (4)

3.2.S.3.2. A discussion of manufacturing issues leading to a series of PMRs is provided in section 3.2.S.2.3.3, Cell Banking. (b) (4) are reviewed in 2.3.S (Quality Overall Summary), 3.2.S.2.5 (Process Validation and/or Evaluation), 3.2.S.3.2 (Impurities), 3.2.S.4.5 (Justification of Specification), 3.2.P.2.2.1 (Formulation Development), 3.2.P.2.3 (Manufacturing Process Development), 3.2.P.5.6 (Justification of Specification), 3.2.A.2 (Adventitious Agents Safety Evaluation), and 3.2.R.2 (Post-Approval Lifecycle Management Plan).

## II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

### a. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

Genentech states that their BLA qualifies for a categorical exclusion from the Environmental Assessment (EA) requirement. Specifically under 21CFR section 25.31(c) any application for marketing approval of a biologic product, or supplement to such an application, is categorically excluded and ordinarily does not require an EA or an Environmental Impact Statement when there is no a significant alteration of the concentration or distribution of the substance, its metabolites or degradation product in the environment. The Sponsor further states that no extraordinary circumstances exist with respect to this product.

### b. PACKAGE INSERT

CMC review and comments on the package insert were provided directly to the team and incorporated into the approved insert.

### c. DRUG PRODUCT LABEL

CMC review of the drug product label was generated under a separate consult to Kimberly Rains, OBP.

## III. LIST OF DEFICIENCIES TO BE COMMUNICATED

There are 7 Post Marketing Requirements (PMRs) and two Post Marketing Commitments (PMCs), which pertain to the CMC aspects of this application. These are listed below.

DMA PMR # 1: Conduct a process validation study to support manufacture of pertuzumab from the Master Cell Bank (MCB (b) (4)) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. Drug substance testing that is part of this qualification must include standard drug substance lot release testing, and analysis of the pertuzumab glycosylation profile, (b) (4), ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the 2012 MCB campaign must be placed into the annual drug substance and drug product stability programs. Concurrent release of process performance qualification (PPQ) batches as per FDA guidance for industry Process Validation: General Principles and Practices must be performed under third party oversight. Submit the final study report as a Prior Approval Supplement (PAS).

DMA PMR #2: Conduct a study that tests the stability of the Master Cell Bank (MCB) at more frequent intervals than the currently proposed 10 years. Submit interim reports every four years and a final report after 20 years.

DMA PMR #3: Conduct a process validation study under third party oversight to support manufacture of pertuzumab from a new Working Cell Bank (WCB) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the

phase 3 clinical trial. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced from the new WCB must include analysis of the (b) (4), ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the new WCB campaign must be placed into the annual drug substance and drug product stability programs. Submit the final study report as a Prior Approval Supplement (PAS).

DMA PMR # 4: Conduct process validation studies under third party oversight to support manufacture of pertuzumab from Working Cell Banks by a modified process using (b) (4) in order to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced by the (b) (4) process must include analysis of the pertuzumab glycosylation profile, (b) (4), ADCC activity, and purity by non-reduced CE-SDS. Submit the final study report as a Prior Approval Supplement (PAS).

DMA PMR # 5: Conduct a stability study that includes real time and stressed stability testing to assess the stability of the drug substance manufactured from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign. The stressed stability testing must be performed prior to release of drug substance arising from thaws #4 and #6 to support comparability of these batches of drug substance to those from the 2010 manufacturing campaign. In addition, one lot of drug substance and drug product arising from both thaws #4 and #6 must be placed on real time stability monitoring. Submit the Interim Report of stressed stability testing as a Changes Being Effected-30 Days (CBE-30).

DMA PMR # 6 Conduct a study using end of production cells from commercial scale manufacturing that tests for in vivo adventitious viruses and genetic consistency. Submit the final study report as a Prior Approval Supplement (PAS).

DMA PMR #7: Conduct a study to establish a drug substance release specification to control for antibody-dependent cellular cytotoxicity (ADCC) activity of pertuzumab (b) (4) and to assess process parameter controls to assure that the process is controlled to maintain ADCC activity within clinical experience. The control strategy must be updated to include ADCC activity and the drug substance release specifications must be updated to include an assay capable of controlling ADCC activity, with acceptance criteria based on clinical experience. In addition, the (b) (4) manufacturing process will need to be updated to include a list of process parameters, and their ranges, sufficient to assure that ADCC activity will remain within clinical experience. Submit the final report as a Prior Approval Supplement (PAS).

DMA PMC # 1 Conduct a study to assess the ability of a non-reduced CE-SDS assay to detect and quantitate pertuzumab fragmentation. If the CE-SDS assay is determined to be non-redundant to the approved SE-HPLC assay, incorporate the CE-SDS assay into the control strategy for pertuzumab and/or the pertuzumab reference standard. Submit the final report as a Changes Being Effected-30 Days (CBE-30).

DMA PMC #2 Reassess release and stability specifications for pertuzumab drug substance and drug product through June 30, 2014.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHRYN E KING  
06/05/2012

LAURIE J GRAHAM  
06/05/2012

BARBARA L RELAHAN  
06/06/2012

WENDY C WEINBERG  
06/06/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration  
Office of Biotechnology Products / Office of Pharmaceutical Science  
Division of Monoclonal Antibodies

## The Quality Team Leaders' Executive Summary

**From:** Wendy C. Weinberg, Ph.D. (Lead)  
Barbara Rellahan, MS, Ph.D. (QbD)  
Division of Monoclonal Antibodies (DMA)

**Through:** Patrick Swann, Ph.D., Deputy Director  
DMA/OBP/OPS/CDER

**BLA Number:** STN 125409

**Product:** Pertuzumab (Perjeta)

**Sponsor:** Genentech, Inc.

**Date of Review:** June 1, 2012

**Due Date of CDTL Memo:** May 18, 2012 (*Note: completion of the Product Quality reviews was delayed due to a series of teleconferences and data submissions through May 24, 2012*)

## I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products, OPS, CDER, does not currently recommend approval of STN 125409 for Pertuzumab manufactured by Genentech. The data submitted in this application are inadequate to support the conclusion that the manufacture of Pertuzumab is well controlled and consistently leads to a product that is pure and potent.

DMA recommends that FDA extend the review clock for 3 months *via* a major amendment mechanism based on any one of a series of submissions received during May, 2012. The CMC team believes this is potentially the fastest pathway to an adequately supported approval of the BLA. This would be expected to enable the applicant to complete their assessment (root cause analysis) of manufacturing problems and determine whether the problems are due to cell bank and/or other process issues, and to determine/define a modified manufacturing process that is appropriately supported with data.

If the review clock will not be extended, DMA's recommendation is a Complete Response (CR) letter, since data have not been provided consistent with a valid commercial manufacturing process.

Based on the understanding that the applicant has refused to make this product more widely available to patients prior to licensure while the manufacturing issues are being addressed, the clinical review office has indicated their intent to approve this product within a time frame consistent with the PDUFA deadline and to resolve outstanding manufacturing issues post-licensure. To the knowledge of the CMC review team, the initial licensure of a biological product under a BLA without concurrent approval of the manufacturing facility and the manufacturing process is unprecedented. This approach was agreed upon by the CDER Director. Therefore, DMA participated in the drafting of PMRs as the only mechanism available to mitigate risks to product quality from a process which lacks adequate validation.

## II. APPROVAL LETTER INFORMATION

Based on discussions with the clinical team, a draft of the approval letter includes language stating that Genentech will not be approved to manufacture pertuzumab drug substance at Genentech in Vacaville, CA until concerns regarding process consistency are resolved (see section III below regarding additional requirements).

The final formulated product will be manufactured, filled, labeled, and packaged at Roche Diagnostics GmbH, Mannheim, Germany. The Sponsor may label pertuzumab with the proprietary name Perjeta and will market it in single-use vials containing 420 mg in 14 mL.

The dating period for pertuzumab drug product shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for pertuzumab drug substance shall be 24 months from the date of manufacture when stored at -20°C. The FDA is approving the stability protocol(s) in the license application for the purpose of extending the expiration dating period of pertuzumab drug substance and drug product under 21 CFR 601.12.

Consistent with 21 CFR 601.12, Genentech must inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved application.

### III. POST MARKETING COMMITMENTS / POST MARKETING REQUIREMENTS

The following PMRs and PMCs were drafted as a mechanism to ensure manufacturing process control after the clinical division indicated that the license would be approved regardless of CMC deficiencies due to the life-threatening indication and unmet need addressed by this product. This text is copied from the most recent version and includes milestone dates sent by Genentech to FDA on June 1, 2012. Additional edits are possible before these are finalized.

#### PMR#1

Conduct a process validation study to support manufacture of pertuzumab from the Master Cell Bank (MCB (b) (4)) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. Drug substance testing that is part of this qualification must include standard drug substance lot release testing, and analysis of the pertuzumab glycosylation profile, (b) (4) ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the 2012 MCB campaign must be placed into the annual drug substance and drug product stability programs. Concurrent release of process performance qualification (PPQ) batches as per FDA guidance for industry Process Validation: General Principles and Practices must be performed under third party oversight. Submit the final study report as a Prior Approval Supplement (PAS).

Study Completion: 12/2012  
 Final Report Submission: 02/2013

#### PMR #2

Conduct a study that tests the stability of the Master Cell Bank (MCB) at more frequent intervals than the currently proposed 10 years. Submit interim reports every four years and a final report after 20 years.

Final Protocol Submission: 09/2012  
 Interim Report 1: 06/2016  
 Interim Report 2: 06/2020  
 Interim Report 3: 06/2024

Interim Report 4: 06/2028

Final Report Submission: 06/2032

### PMR #3

Conduct a process validation study under third party oversight to support manufacture of pertuzumab from a new Working Cell Bank (WCB) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced from the new WCB must include analysis of the (b) (4), ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the new WCB campaign must be placed into the annual drug substance and drug product stability programs. Submit the final study report as a Prior Approval Supplement (PAS).

Final Protocol Submission: 04/2013

Study Completion: 09/2014

Final Report Submission: 10/2014

### PMR #4

Conduct process validation studies under third party oversight to support manufacture of pertuzumab from Working Cell Banks by a modified process (b) (4) in order to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced by the (b) (4) process must include analysis of the pertuzumab glycosylation profile, (b) (4) ADCC activity, and purity by non-reduced CE-SDS. Submit the final study report as a Prior Approval Supplement (PAS).

Final Protocol Submission: 04/2014

Study Completion: 10/2015

Final Report Submission: 11/2015

### PMR #5

Conduct a stability study that includes real time and stressed stability testing to assess the stability of the drug substance manufactured from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign. The stressed stability testing must be performed prior to release of drug substance arising from thaws #4 and #6 to support comparability of these batches of drug substance to those from the 2010 manufacturing campaign. In addition, one lot of drug substance and drug product arising from both thaws #4 and #6 must be placed on real time

stability monitoring. Submit the Interim Report of stressed stability testing as a Changes Being Effected-30 Days (CBE-30).

Final Protocol Submission: 06/2012  
Interim Report (Stressed): 09/2012  
Study Completion: 10/2014  
Final Report (Real Time): 12/2014

#### **PMR #6**

Conduct a study using end of production cells from commercial scale manufacturing that tests for in vivo adventitious viruses and genetic consistency. Submit the final study report as a Prior Approval Supplement (PAS).

Final Protocol Submission: 08/2012  
Study Completion: 12/2012  
Final Report Submission: 02/2013

#### **PMR #7**

Conduct a study to establish a drug substance release specification to control for antibody-dependent cellular cytotoxicity (ADCC) activity of pertuzumab (b) (4) and to assess process parameter controls to assure that the process is controlled to maintain ADCC activity within clinical experience. The control strategy must be updated to include ADCC activity and the drug substance release specifications will be updated to include an assay capable of controlling ADCC activity, with acceptance criteria based on clinical experience. In addition, the (b) (4) manufacturing process will need to be updated to include a list of process parameters, and their ranges, sufficient to assure that ADCC activity will remain within clinical experience. Submit the final report as a Prior Approval Supplement (PAS).

Study Completion: 02/2013  
Final Report Submission: 03/2013

#### **PMC #1**

Conduct a study to assess the ability of a non-reduced CE-SDS assay to detect and quantitate pertuzumab fragmentation. If the CE-SDS assay is determined to be non-redundant to the approved SE-HPLC assay, incorporate the CE-SDS assay into the control strategy for pertuzumab and/or the pertuzumab reference standard. Submit the final report as a Changes Being Effected-30 Days (CBE-30).

Final Protocol Submission: 09/2012  
Study Completion: 07/2013  
Final Report Submission: 09/2013

#### **PMC #2**

Reassess release and stability specifications for pertuzumab drug substance and drug product through June 30, 2014.

Final Protocol Submission: N/A  
Study Completion: 12/2014  
Final Report Submission: 03/2015

#### IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

Refer to the list of PMRs and PMCs in section III designed to address deficiencies post-licensure.

#### V. EXECUTIVE SUMMARY

##### ***A. Description of Pertuzumab (Perjeta) drug substance and drug product***

Pertuzumab is a full length recombinant, humanized, immunoglobulin IgG1 $\kappa$  monoclonal antibody (rhuMAB 2C4; Omnitarg; 2C4) that is directed to subdomain II of the human epidermal growth factor receptor 2. Pertuzumab is comprised of two heavy chains (448 or 449 amino acid residues, dependent on the presence of a C-terminal lysine) and two light chains (214 amino acid residues), and contains an N-linked oligosaccharide. The total molecular weight of pertuzumab is approximately 148,000 Da, (b) (4)

The human epidermal growth factor receptor 2 (EGF-R2, HER2, c-erbB-2) is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Amplification and/or overexpression of HER2 has been reported in 15-25% of breast cancers and is associated with increased tumor aggressiveness, higher rates of recurrence, and increased mortality. Pertuzumab is used in combination with trastuzumab and docetaxel to treat patients with HER2-positive metastatic breast cancer who have not already received anti-HER2 therapy or chemotherapy for metastatic disease.

Pertuzumab drug product is supplied as a sterile, preservative-free liquid formulation at 30 mg/ml. Pertuzumab drug product is formulated in 20mM L-histidine acetate, 120mM sucrose, and 0.02% (w/v) polysorbate 20, pH 6.0. (b) (4)

As supplied, the solution of pertuzumab drug product has a clear to slightly opalescent, colorless to pale brown appearance. It is supplied in single-use, 20 ml vials containing 420 mg (nominal) pertuzumab for intravenous (IV) infusion. The extractable volume of each vial is 14 ml.

The intended long term storage temperature for pertuzumab drug product is 2-8°C.

The primary packaging components for pertuzumab drug product consist of a USP/Ph. Eur./JP (b) (4) 20 ml colorless glass vial that is sealed (b) (4) rubber stopper (b) (4) and crimped with a 20mm aluminum seal, then fitted with a slip off plastic cap.

The pertuzumab drug product vial [REDACTED] (b) (4)

Pertuzumab is diluted into a 250 ml 0.9% saline IV bag immediately prior to administration. The diluted infusion solution can be stored at 2-8°C for up to 24 hours.

A claim for a categorical exclusion from the Environmental Assessment (EA) requirement has been submitted under 21CFR section 25.31(c), which states that any application for marketing approval of a biologic product for substances that occur naturally in the environment, or supplement to such an application, is categorically excluded and ordinarily does not require an EA or an Environmental Impact Statement when there is not a significant alteration of the concentration or distribution of the substance, its metabolites or degradation product in the environment. The Sponsor states that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

### ***B. Clinical Trial Information***

Pertuzumab is intended as first-line treatment of patients with HER2 positive metastatic or locally recurrent unresectable breast cancer, who have not received previous treatment, or whose disease has relapsed after adjuvant therapy. It is intended to be administered in combination with trastuzumab and docetaxel.

The route of administration of pertuzumab is IV infusion. The recommended dosing is a loading dose of 840 mg (60 min infusion), followed by 420 mg (30-60 minute infusion) every 3 weeks thereafter, until disease progression or unacceptable toxicity.

Patients should be selected based on positive HER2 protein overexpression. Patients in the randomized trial had demonstrated HER2 overexpression as determined by Dako Herceptest or Dako HER2 FISH PharmDx test kit.

Genentech has performed three clinical studies to evaluate pertuzumab plus trastuzumab and docetaxel (Pertuzumab/T/D) in HER2-positive breast cancer, in comparison to the standard of care, trastuzumab and docetaxel alone. The pivotal Phase III study WO20698/TOC4129g was a randomized, double-blind, placebo-controlled multicenter study of 808 patients with untreated HER2-positive locally recurrent, unresectable or metastatic breast cancer treated with Pertuzumab/T/D vs. Placebo/T/D. The primary objective was to compare progression free survival (PFS). The Sponsor reported an increase in median PFS of 6.1 months in the Pertuzumab-containing treatment group.

This BLA was granted priority review status.

### ***C. Stability***

Pertuzumab is supplied in single-use vials without preservatives.

Drug substance: Real time stability data were provided following 18 months storage of the conformance lots, and in conjunction with 48 months of real-time stability data from drug substance lots manufactured at (b) (4) that were deemed comparable to drug substance manufactured at Vacaville, support long term storage at the recommended temperature of -20°C for the proposed dating period of 24 months.

Drug product: Real time stability data were provided following 18 months storage of the conformance lots, and in conjunction with 48 months real time stability data from lots manufactured at (b) (4) that were deemed comparable to drug product manufactured at Mannheim, support long term storage at the recommended temperature of 2-8°C for the proposed dating period of 24 months.

The most sensitive stability-indicating assay identified for pertuzumab is IE-HPLC, which demonstrates (b) (4) under accelerated (40°C) conditions. Changes in the charge variant profile are also readily detected by IE-HPLC following intense light, oxidation, and degradation by acid and base. SE-HPLC is also a sensitive stability-indicating assay, for which the (b) (4) slightly under accelerated (40°C) conditions. Aggregation/fragmentation can be detected by SE-HPLC and CE-SDS on reduced samples of pertuzumab which were subjected to elevated temperature, intense light, oxidation and degradation by acid/base.

Development studies indicated that the optimal pH for pertuzumab is pH 6.0, as determined by CZE and IE-HPLC. The impact of thermal stress (40°C), light exposure (1.2 x 10(6) lux hours), oxidation and pH changes (pH 3.2, 8.5) on biological activity of pertuzumab drug substance was assessed. No significant changes were observed on the anti-proliferative activity of pertuzumab or its ability to bind HER2 (b) (4), however a trend toward lower (b) (4) was detected in response to light and altered pH (both acidic and basic).

Pertuzumab drug substance has been shown to be stable through multiple freeze/thaw cycles. A photostability study indicated that drug product should be protected from direct light. The package insert states that the drug product should be protected from light, and not frozen or shaken.

## ***D. Complexity***

### **Critical Quality Attributes (Written by BR)**

The sponsor used a risk based approach to identify quality attributes which can impact the safety and/or efficacy of the product (i.e., critical quality attributes (CQAs)). The risk based approach used a risk ranking and filtering (RRF) tool to evaluate the severity and the uncertainty associated with each quality attribute's potential to impact product safety and/or efficacy. The evaluation used product specific information, as well as platform and publicly available information to inform the risk assessment. The severity or 'impact' assessment included potential product impact to bioactivity, pharmacokinetics, immunogenicity and safety. Uncertainty was assessed using five ranking scores which ranged from 1-7, with 1 being very low uncertainty and 7 being very high. The severity and uncertainty scores were multiplied to calculate a final risk score for each attribute. Attributes with a risk score above a specified value

(i.e., 13) were classified as critical quality attributes. The BLA contained sufficient information to explain and justify the RRF and scoring system used. The proposed summary list of CQAs identified by the sponsor are listed below in a, Table 3.2.S.3.2-29, which was copied directly from the submission.

Table 3.2.S.3.2-29 Summary of Pertuzumab Critical Quality Attributes

(b) (4)



While it was felt that the RRF and scoring matrix used was appropriate, several issues were identified where it was thought that the severity or uncertainty risk assessment was not performed appropriately. Examples are:

- *In vitro* assays have demonstrated that pertuzumab can mediate tumor cell death via antibody dependent cellular cytotoxicity (ADCC). The sponsor concluded however that ADCC was not a mechanism of action of the pertuzumab based on xenograft animal models in which pertuzumab molecules lacking an Fc-domain were shown to be effective at reducing tumor growth. Based on the sponsor's conclusion that ADCC was not a mechanism of action, quality attributes such as glycosylation which have the potential to impact ADCC activity but not inhibition of proliferation, antibody pharmacokinetics (PK), safety or immunogenicity were given low severity scores. After consultation with the pre-clinical review team, it was determined that the animal models were not sufficiently sensitive/representative to demonstrate that ADCC does not contribute to pertuzumab efficacy and the Agency considers ADCC a potential mechanism of action for pertuzumab. Quality attributes which have the potential to impact ADCC activity should, therefore, have been considered CQAs.
- When evaluating the immunogenicity impact of a number of quality attributes, the sponsor based their assessment on pertuzumab immunogenicity rates observed in the clinic rather than on available knowledge on the overall likelihood of the attribute to impact immunogenicity. Many of the attributes that were assessed in this manner were

present in very small amounts in pertuzumab drug product and so clinical data from the pertuzumab trials was highly unlikely to reflect the true immunogenic potential of the attribute. Many of the attributes that were impacted by this assessment however, were classified as a CQA based on other parameters and in the end, it was not thought that this risk assessment deficiency had a significant impact on the final list of CQAs which were identified. This approach however, could impact post-approval management of quality attributes and should be resolved prior to Agency approval of a (b) (4)

- The raw material and leachate risk assessment took process capability into account and since process-related impurities are well controlled by the process, no raw materials or leachates were identified as CQAs. A raw material daily intake risk assessment was provided. Since process capability was not supposed to be a component of the CQA risk assessment, its consideration when assessing raw material and leachate risk was inappropriate. Upon request, the sponsor justified their strategy indicating that a strict application of the CQA definition is not appropriate in this case since it would generate a large number of CQAs which would then impact the control strategy, validation activities, and significantly increase the periodic monitoring testing requirements. Because the process was shown to provide robust control over raw materials, the issue of how to classify raw materials was not further addressed during the original BLA review cycle but may need to be prior to Agency approval of a (b) (4)

### Control Strategy

The proposed control strategy for in-process, release, stability and comparability testing for pertuzumab drug substance and drug product was also based on (b) (4), and proposed specifications were based on (b) (4) as well as data from 11 drug substance batches manufactured at the commercial scale at Vacaville (2010 campaign) and (b) (4) (2007). The testing requirements and acceptance criteria were not deemed sufficient by either a (b) (4) traditional approach. Following information requests and teleconferences, the Sponsor made the following commitments regarding the need for additional testing:

- Evaluate the use of non-reduced CE-SDS for detection of fragments, or provide justification that the SE-HPLC method is adequate for evaluation of LMWS (refer to PMR, section III),
- Incorporate a measure of ADCC activity into the drug substance control strategy. This is to include developing a validated assay for (b) (4) as a product quality attribute linked to ADCC, in conjunction with characterization studies from (b) (4) manufacturing for control of ADCC (refer to PMR), In the meantime, monitor (b) (4) in drug substance, with an interim limit defined of (b) (4)

Furthermore, many of the proposed acceptance criteria were outside of manufacturing and clinical experience. During discussions the Sponsor committed to tightening the rejection limit for in process drug substance IE-HPLC testing and drug product lot release and stability IE-HPLC testing based on manufacturing experience. The Agency agreed that the drug substance test could remain an in-process test based on a commitment from the Sponsor to inform the Agency through a BLA supplement if any changes are made to the rejection limits. In addition,

the Sponsor committed to tightening the acceptance criteria for subvisible particulates for drug product release and stability testing. From a safety and efficacy standpoint, it was determined by the CMC reviewers that the release and stability testing as agreed upon during the BLA review are adequate to assure product quality. However, from the perspective of process consistency, the Agency determined these criteria should be based more on manufacturing experience, and should be reassessed as more experience is gained (see PMC #2). In addition, quantitative criteria should be set for glycans (b) (4). As the (b) (4) review team concluded that the BLA did not contain sufficient information to support the (b) (4), and insufficient assurance was provided that the most appropriate testing would be included to support manufacturing changes, comparability protocols will need to be reviewed for acceptability through a post-approval mechanism.

With regard to control strategy, data provided by the Sponsor indicated the following links between product characteristics and activity:



Control over impurities was deemed adequate. Clearance of (b) (4) was established by process validation.

### ***E. Mechanism of Action***

The primary mechanism of action of pertuzumab is through its binding to the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein

(HER2). HER2 is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. It is one of 4 members of the human EGFR family which also includes EGFR (HER1), HER3 and HER4. The EGFR family members function as homo- or heterodimers. HER signaling is known to play roles in neoplastic cell growth, malignant transformation and resistance to chemotherapy. Ligand-initiated heterodimerization of HER2 with other family members leads to signaling through the mitogen-activated protein (MAP) kinase and phosphoinositide-3-kinase (PI3K) pathways. By binding to subdomain II of HER2, pertuzumab blocks this dimerization and the downstream MAPK and PI3K signaling pathways, leading to cell growth arrest and apoptosis, respectively.

Pertuzumab is an IgG1 $\kappa$  and is therefore expected to have activity in mediating antibody-dependent cell-mediated cytotoxicity (ADCC), an additional mechanism of action claimed in several locations throughout the BLA. However, in the drug substance characterization section, the Sponsor states that ADCC may not always be necessary for the *in vivo* activity of pertuzumab. As this statement was not sufficiently supported by data, the Agency has asked that control be established for attributes of pertuzumab that are correlated with ADCC activity (refer to section III of this summary).

Note: Pertuzumab is administered in conjunction with trastuzumab, another IgG $\kappa$ 1 antibody that was licensed by Genentech in 1998 and binds to a distinct epitope on HER2. Trastuzumab binds to subdomain IV of the extracellular domain of HER2 and disrupts ligand-independent interactions of HER2. Unlike pertuzumab, it is not effective in blocking dimerization of HER2 with ligand-activated family members EGFR, HER3 or HER4, but also results in inhibition of downstream signaling events. Like pertuzumab, trastuzumab is also capable of mediating ADCC activity. In addition, trastuzumab, by binding to domain IV, blocks a proteolytic cleavage site on the HER2 ectodomain and the resulting generation of phosphorylated p95 and constitutive activation of the intracellular kinase domains. Pertuzumab does not share this activity with trastuzumab.

The potency assay for pertuzumab is

(b) (4)

(b) (4)

## **F. Manufacturing Process**

The drug substance manufacturing site is Genentech, Inc. in Vacaville, CA.

(b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WENDY C WEINBERG  
06/04/2012

BARBARA L RELAHAN  
06/04/2012

PATRICK G SWANN  
06/05/2012

PATRICK G SWANN on behalf of KATHLEEN A CLOUSE STREBEL  
06/05/2012

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

## Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing<sup>1</sup> locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

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## APPLICATION INFORMATION

PDUFA Action Date: June 8, 2012

Applicant Name: Genentech, Inc.

U.S. License #: 1048

STN(s): 125409/0

Product(s): Perjeta (pertuzumab)

Short summary of application: PERJETA is a HER2/neu receptor antagonist hughindicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

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## FACILITY INFORMATION

Manufacturing Location:

Firm Name: Genentech

Address: 1000 New Horizons Way, Vacaville, CA 95688-9431

FEI: 3002902534

Short summary of manufacturing activities performed:

Manufacture batch release testing (Drug Substnace)

Manufacturing Location:

Firm Name: Roche Diagnostics GmbH

Address: Sandhoferstrasse 116, 68305 Mannheim Germany

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<sup>1</sup>The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

FEI: 3002806559

Short summary of manufacturing activities performed:  
Manufacture batch release testing (Drug Product)



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AMY R TILLEY  
05/24/2012