

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125409Orig1s0051

OTHER REVIEW(S)

PMR Development Template

This template should be completed by the PMR Development Coordinator and included for ***each*** PMR in the Action Package.

BLA # sBLA 125409\51
Product Name: Pertuzumab (Perjeta®)

PMR 1 Description: Submit the final efficacy (disease-free survival) and safety results from Trial BO25126 (APHINITY) as defined in your protocol and Statistical Analysis Plan (SAP).

<u>PMR</u> Schedule Milestones:	Final Protocol Submission:	<u>10/2013</u>
	Trial Completion:	<u>11/2016</u>
	Final Report Submission:	<u>05/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/ instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Genentech proposes to use the ongoing APHINITY trial as the confirmatory trial to support the conversion from accelerated approval to regular approval for pertuzumab in the neo-adjuvant setting. This adjuvant trial is a randomized controlled trial in 4800 women with HER2-positive early breast cancer designed to demonstrate the superiority of adjuvant pertuzumab plus trastuzumab in combination with standard chemotherapy compared to placebo pertuzumab plus trastuzumab and standard chemotherapy with regard to the primary endpoint disease-free survival from invasive breast cancer. This trial will also provide information to better characterize the overall toxicity profile of pertuzumab in the early breast cancer population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The ongoing APHINITY trial, if positive, will provide the confirmatory evidence of clinical benefit to support the conversion of use of pertuzumab in the neo-adjuvant setting from accelerated approval to full approval. This trial will also provide information to better characterize the overall toxicity profile of pertuzumab in the early breast cancer population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The APHINITY adjuvant trial is an ongoing randomized controlled trial in 4800 women with HER2-positive early breast cancer designed to demonstrate the superiority of adjuvant pertuzumab plus trastuzumab in combination with standard chemotherapy compared to placebo pertuzumab plus trastuzumab and standard chemotherapy with regard to the primary endpoint of disease-free survival from invasive breast cancer.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMR? Yes
 - Are the objectives clear from the description of the PMR? Yes
 - Has the applicant adequately justified the choice of schedule milestone dates? Yes
 - Has the applicant had sufficient time to review the PMR, ask questions, determine feasibility, and contribute to the development process? Yes
-

PMR Development Coordinator:

- This PMR has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Genevieve Schechter, M.D.
Acting Deputy Director for Safety, DOP1

PMR Development Template

This template should be completed by the PMR Development Coordinator and included for each PMR in the Action Package.

BLA # sBLA # 125409\51
Product Name: Pertuzumab (Perjeta®)

PMR 2 Description: Conduct a clinical trial to further assess the cardiac safety of neoadjuvant anthracycline/taxane-based chemotherapy regimens when administered in combination with neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer.

PMR Schedule Milestones:	Final Protocol Submission:	<u>01/2014</u>
	Trial Completion:	<u>08/2016</u>
	Final Report Submission:	<u>02/2017</u>

1. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The NEOSPHERE and TRYPHAENA trials showed an increase rate of left ventricular dysfunction with the addition of pertuzumab. Most cases of cardiac dysfunction were asymptomatic and reversible; however, the cardiac safety profile of pertuzumab and trastuzumab in combination with chemotherapy regimens commonly used in the USA needs to be evaluated. This is of particular importance due to the longer life expectancy in the early breast cancer population as compared to the metastatic breast cancer population. This PMR trial will evaluate the cardiac and overall safety of two different neoadjuvant pertuzumab and anthracycline-containing regimens using a parallel two cohort trial design.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Pertuzumab in combination with trastuzumab is associated with increased cardiac toxicity. This trial will evaluate the cardiac safety of pertuzumab and trastuzumab used in combination with chemotherapy regimens commonly used in the USA. This PMR trial will look at the cardiac and overall safety of two different neoadjuvant pertuzumab and trastuzumab anthracycline-containing regimens using a parallel two cohort trial design.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The clinical trial is required to further assess the cardiac safety of neoadjuvant anthracycline/taxane-based chemotherapy regimens when administered in combination with neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs? Yes

Are the objectives clear from the description of the PMR? Yes

Has the applicant adequately justified the choice of schedule milestone dates? Yes

Has the applicant had sufficient time to review the PMRs, ask questions, determine feasibility, and contribute to the development process? Yes

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR Development Coordinator:

This PMR has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Genevieve Schechter, M.D.

Acting Deputy Director for Safety, DOP1

PMC Development Template

This template should be completed by the PMC Development Coordinator and included for each PMC in the Action Package.

BLA # sBLA#125409\51,
Product Name: Pertuzumab (Perjeta®)

PMC 3 Description: Submit the final event-free survival (EFS) analysis of trial WO20697 (NEOSPHERE).

PMC Schedule Milestones:	Final Protocol Submission:	<u>10/2013</u>
	Trial Completion:	<u>11/2014</u>
	Final Report Submission:	<u>03/2015</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The final event-free survival (EFS) results of trial WO20697 (NEOSPHERE) will, if significant, provide support for the pathological complete response (pCR) result favoring the pertuzumab treatment arm in the NEOSPHERE trial.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The final event-free survival (EFS) results of trial WO20697 (NEOSPHERE), if significant, will provide support for the pathological complete response results favoring the pertuzumab treatment arm in the NEOSPHERE trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMC requests that the final event-free survival (EFS) analysis information from the ongoing Trial WO20697 (NEOSPHERE) be submitted. The trial results will provide additional information regarding the use of pCR in early breast cancer (neoadjuvant setting).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for a PMCs? Yes

Are the objectives clear from the description of the PMC? Yes

Has the applicant adequately justified the choice of schedule milestone dates? Yes

Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMC Development Coordinator:

This PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Genevieve Schechter, M.D.

Acting Deputy Director for Safety, DOP1

PMC Development Template

This template should be completed by the PMC Development Coordinator and included for each PMC in the Action Package.

BLA # sBLA#125409\51, Pertuzumab (Perjeta®)
Product Name: _____

PMC 4 Description: Conduct a study of pretreatment molecular subtyping of tumors from patients treated in the postmarketing cardiac safety trial (PMR#2) and submit an exploratory analysis of the relationship of pathological complete response with the different tumor subtypes.

PMC Schedule Milestones:	Final Protocol Submission:	01/2014
	Study/Trial Completion:	08/2016
	Final Report Submission:	08/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

HER2-positive breast cancer is very heterogeneous. Data from prior trials in which patients with different HER2-positive tumor subtypes were enrolled suggest differing sensitivities to HER2 targeted agents depending on the tumor molecular subtype. This may impact the pathological complete response (pCR) endpoint. Pretreatment molecular subtyping of HER2+ tumors will assist the clinician in identifying patients who are at higher risk of failing to attain a pCR with pertuzumab combination therapies and who are at higher risk of relapse and death despite therapy with pertuzumab containing regimens. In addition, information about tumor molecular subtyping and sensitivity to HER2 targeted therapies will provide information for the selection of patients to be included in future trials using HER2+ directed agents.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Data from prior trials that enrolled patients with different HER2-positive tumor subtypes (determined molecularly) suggests that differing molecular subtypes have differing sensitivities to HER2 targeted agents, which may impact pathological complete response (pCR). Pretreatment molecular tumor subtyping will address this issue and provide clinicians with information to identify patients who are at higher risk of failing to attain a pCR, and who are at higher risk of relapse and death despite therapy with pertuzumab containing regimens. This information will also help informed the selection of patients for future trials using HER2+ targeting agents.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The applicant agreed to conduct a study of pretreatment molecular subtyping of tumors from patients treated in the postmarketing cardiac safety trial and submit an exploratory analysis of the relationship of pathological complete response with the different tumor subtypes.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

Clinical study to evaluate the relationship of HER2+ breast cancer tumor subtypes with tumor response.

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Genevieve Schechter, M.D.

Acting Deputy Director for Safety, DOP1

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

/s/

AMY R TILLEY
09/25/2013

GENEVIEVE A SCHECHTER
09/25/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)**

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

Memorandum

Date: September 25, 2013

To: Amy Tilley – Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD – Regulatory Review Officer
OPDP

Subject: OPDP comments on draft product labeling for Perjeta (pertuzumab) injection
(Perjeta)
BLA 125409

As requested in your consult dated May 16, 2013, OPDP has reviewed the draft labeling, Package Insert (PI) for Perjeta.

OPDP provided the following comments via email based on the proposed September 6, 2013 version of the PI:

Section	Statement from draft	Comment
<ul style="list-style-type: none">5.4 Hypersensitivity Reactions/ Anaphylaxis		
<ul style="list-style-type: none">6.1 Clinical Trials Experience		
<ul style="list-style-type: none">6.1 Neoadjuvant Treatment of Breast Cancer		

(b) (4)

	(b) (4)
<ul style="list-style-type: none">• 12.1 Mechanism of Action	

OPDP has no further comments on the September 25, 2013 version of the PI.

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

/s/

MARYBETH TOSCANO
09/25/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 27, 2013

TO: Amy Tilley, Regulatory Health Project Manager
Laleh Amiri-Kordestani, M.D., Medical Officer
Suparna Wedam, M.D., Medical Officer
Division of Oncology Products 1

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

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125409s51
APPLICANT: Genentech, Inc.

DRUG: Pertuzumab (Perjeta[®])

NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the neoadjuvant treatment of HER2-positive breast cancer.

CONSULTATION REQUEST DATE: June 6, 2013
INSPECTION SUMMARY GOAL DATE: September 16, 2013
DIVISION ACTION GOAL DATE: September 30, 2013
PDUFA DATE: October 31, 2013

I. BACKGROUND:

Genentech, Inc., seeks approval to expand the use of pertuzumab to include the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide (FEC), or carboplatin. Pertuzumab was first approved by FDA for marketing in the United States for the treatment of HER2-positive metastatic breast cancer on June 8, 2012.

Pertuzumab is a recombinant, humanized, IgG κ monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. By binding to the extracellular domain of HER2, pertuzumab prevents heterodimerization of HER2 with other members of the HER family, which is likely contributing to slowed tumor growth. The application is based largely on the results of the pivotal Phase 2 Study WO20697 (NEOSPHERE), a study solely conducted outside of the United States.

Study WO20697 (NEOSPHERE) was initiated in 2007 and remains ongoing. It is a randomized, multicenter, multinational open-label study. The study was designed to compare the dual activity of pertuzumab and trastuzumab with the activity of either antibody alone, in combination with docetaxel, as well as to assess the activity of trastuzumab and pertuzumab in the absence of docetaxel. A total of 400 study subjects were planned and 417 study subjects were randomized to one of 4 neoadjuvant therapy treatment arms: 107 subjects in trastuzumab and docetaxel (Arm A), 107 subjects in trastuzumab, pertuzumab, and docetaxel (Arm B), 107 subjects in trastuzumab and pertuzumab (Arm C), and 96 subjects in pertuzumab and docetaxel (Arm D). The study was conducted at 56 centers in 16 countries. This study was not conducted under an IND.

Three clinical sites were chosen for inspection: Site 116798 (Dr. Luca Gianni, Milano, Italy), Site 116801 (Dr. Tadeusz Pienkowski, Warszawa, Poland), and Site 116814 (Dr. Ana Lluçà Hernandez, Valencia, Spain, based on enrollment of large numbers of study subjects).

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Giulia V. Bianchi, M.D. (Current CI) Luca Gianni, M.D. (Former CI) Istituto Nazionale Per Lo Studio E La Cura Dei Tumori Milano, Italy	Protocol: WO20697 Site Number: 116798 Number of Subjects: 28	July 29, 2013 - August 2, 2013	Pending Interim classification: VAI
CI#2: Tadeusz Pienkowski, M.D. Centrum Onkologii-Inst. Im. MarII Skłodowskiej-Curie Warszawa, Poland	Protocol: WO20697 Site Number: 116801 Number of Subjects: 28	July 29, 2013 - August 2, 2013	Pending Interim classification: NAI
CI#3: Ana Lluch Hernandez, M.D. Hospital Clinico Universitario de Valencia Valencia, Spain	Protocol: WO20697 Site Number: 116814 Number of Subjects: 16	July 29, 2013 – August 3, 2013	Pending Interim classification: NAI

Key to 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.

1. CI#1: – Giulia V. Bianchi, M.D.

Istituto Nazionale Per
Lo Studio E La Cura Dei Tumori
Milano, Italy

- a. What was inspected:** The site screened 33 subjects, 28 subjects were enrolled, and 27 completed the study. The study records of 10 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to electronic CRFs (eCRFs) and data listings submitted to BLA 125409 s51, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring reports, and financial disclosure forms.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoint for the study was complete pathologic response, defined as the absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. The source records audited at this site supported and corroborated with the site investigator-reported response rates. There was no evidence of underreporting of adverse events. The FDA field investigator found occasional use of pertuzumab and trastuzumab from inappropriate sources. Specifically, the site had administered the investigational drug, pertuzumab, provided to the site for another Roche-sponsored investigational study that also used pertuzumab, to two subjects enrolled in the Roche WO20697 clinical study over a two day period. In addition, on at least ten occasions commercial product trastuzumab was administered to study subjects when the site pharmacy did not have enough investigational trastuzumab in stock for Study WO20697. The FDA field investigator issued a one item FDA Form 483, Inspectional Observations.

1. Investigational drug disposition records are not adequate with respect to use by subjects.

Specifically,

- a. On 10/28/08 five vials of investigational pertuzumab from Protocol BO17979 were dispensed and administered to Subject #2287. Subject #2287 was enrolled in Study WO20697.
- b. On 10/29/08 three vials of investigational pertuzumab from Protocol BO17979 were dispensed and administered to Subject #2312. Subject #2312 was enrolled in Study WO20697.
- c. On ten occasions in 2008, 2009, and 2010 vials of commercial product trastuzumab was administered to subjects in place of investigational product trastuzumab during Study WO20697. For example,
 - 1) Three vials of commercial product of trastuzumab (Batch# unknown) were administered to Subject #2285 on 10/19/10.
 - 2) Two vials of commercial product of trastuzumab (Batch# unknown) were administered to Subject #2319 on 2/18/10.
 - 3) Three vials of commercial product of trastuzumab (Batch# unknown) were administered to Subject #2283 on 12/10/08.
 - 4) Commercial product vials of trastuzumab (Batch #HO5838B01) were administered to Subject #2309 on 4/14/09 and Subject #2307 on 4/15/09.
 - 5) Commercial product vials of trastuzumab (Batch #H3113B01) were administered to Subject #2311 and Subject #2313 on 10/27/09.
 - 6) Commercial product vials of trastuzumab (Batch #HO605B01) were administered to Subject #2319 and Subject #2281 on 10/27/09.

- 7) Commercial product vials of trastuzumab (Batch #HO3078B01) were administered to Subject #2308 on 10/22/08.

OSI Reviewer Notes: *The FDA field investigator found that overall the site conducted the study very well. However, it was discovered that on several occasions the site administered the study medication pertuzumab to subjects in Study WO20697 that was provided to the site by the sponsor for use in a different investigational study. On numerous occasions the site administered commercially available trastuzumab to subjects in Study WO20697 when the local pharmacy apparently did not have enough investigational trastuzumab in stock. While these are valid inspectional observations, which must be addressed and corrected by this site, they should not importantly impact data generated by this site.*

- c. Assessment of data integrity:** The data for Dr. Bianchi's site, associated with Study WO20697 submitted to the Agency in support of BLA 125409 s51, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: – Tadeusz Pienkowski, M.D.

Centrum Onkologii-Inst. Im. MarII Sklodowskiej-Curie
Warszawa, Poland

- a. What was inspected:** The site screened 47 subjects, 28 subjects were enrolled, and 22 completed the study. Portions of the study records of all subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs and data listings submitted to BLA 125409 s51, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring reports, and financial disclosure forms.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoint for the study was complete pathologic response, defined as the absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. The source records audited at this site supported and corroborated with the site investigator-reported response rates. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. With a few minor exceptions adverse events were adequately reported. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Pienkowski's site, associated with Study WO20697 submitted to the Agency in support of BLA 125409 s51, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. CI#3: – Ana Lluch Hernandez, M.D.
Hospital Clinico Universitario de Valencia
Valencia, Spain

- a. What was inspected:** The site screened 23 subjects, 16 subjects were enrolled, and 13 completed the study. The study records of 23 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs and data listings submitted to BLA 125409 s51, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring reports, and financial disclosure forms.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. Per the protocol, the primary efficacy endpoint for the study was complete pathologic response, defined as the absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. The source records audited at this site supported and corroborated with the site investigator-reported response rates. With one exception, adverse events were adequately reported. Briefly, Subject #3812 visited the Emergency Room on (b) (6) (in between study visits 2 and 3) due to fever and chills. Subject #3812 was diagnosed with pneumonia, confirmed by x-rays, and was prescribed antibiotics (Augmentin and Tavanic). This AE and the concomitant medications were not reported in the subject's eCRF by the site. Dr. Hernandez explained that in 2009 the subject's medical history/chart was still on hard copy and as such the information was not readily available to other medical departments in real-time. In practice, the study staff would learn of "out of visit AEs", such as this example, during a subject's interview at the subsequent study visit. In this case, apparently Subject #3812 did not inform the site staff of the ER visit, and subsequent diagnosis and treatment. Dr. Hernandez explained that this incident is currently very unlikely to happen at this clinic because the hospital transitioned to electronic medical records, available now to all departments, a couple of years ago. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Hernandez' site, associated with Study WO20697 submitted to the Agency in support of BLA 125409 s51, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Giulia V. Bianchi (Site 116798), Dr. Tadeusz Pienkowski (Site 116801), and Dr. Ana Lluch Hernandez (Site 116814), the Study WO20697 data appear reliable based on available information.

One clinical site inspected, Dr. Giulia V. Bianchi (Site 116798) was issued a Form FDA 483 citing inspectional observations, and the preliminary classification for this inspection is Voluntary Action Indicated (VAI). The preliminary classifications for the remaining inspections of Dr. Tadeusz Pienkowski (Site 116801), and Dr. Ana Lluch Hernandez (Site 116814), are No Action Indicated (NAI).

The inspection of Dr. Bianchi's site (116798) found occasional use of pertuzumab and trastuzumab from inappropriate sources. Specifically, the firm had administered investigational drug, pertuzumab, provided to the site for another Roche-sponsored investigational study that also used pertuzumab, to two subjects enrolled in the Roche WO20697 clinical study over a two day period. In addition, on at least ten occasions commercial product trastuzumab was administered to study subjects when the site pharmacy apparently did not have enough investigational trastuzumab in stock for Study WO20697. While these are valid inspectional observations, which must be addressed and corrected by this site, they should not importantly impact data generated by this site.

Finally, regarding Dr. Hernandez' site (116814), there was one adverse event discrepancy between source documentation and data listings submitted to BLA 125409 s51. Specifically, Subject #3812 visited the Emergency Room on [REDACTED] (b) (6) (in between study visits 2 and 3) due to fever and chills. Subject #3812 was diagnosed with pneumonia, confirmed by x-rays, and was prescribed antibiotics (Augmentin and Tavanic). This AE and the concomitant medications were not reported in the subject's eCRF by the site. Dr. Hernandez explained that in 2009 the subject's medical history/chart was still on hard copy and as such the information was not readily available to other medical departments in real-time. In practice, the study staff would learn of "out of visit AEs", such as this example, during a subject's interview at the subsequent study visit. In this case, apparently Subject #3812 did not inform the site staff of the ER visit, and subsequent diagnosis and treatment.

Although regulatory violations were noted as described above, they are unlikely to importantly impact primary safety and efficacy analyses. The overall data for Study WO20697 (NEOSPHERE) in support of this application may be considered reliable based on available information.

Note: The observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

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

/s/

LAUREN C IACONO-CONNORS
08/27/2013

JANICE K POHLMAN
08/27/2013

SUSAN D THOMPSON
08/27/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125409	NDA Supplement #:S- BLA Supplement # 051	Efficacy Supplement Type SE- 1
Proprietary Name: Perjeta Established/Proper Name: pertuzumab Dosage Form: Single-use vial Strengths: 420 mg/14 mL		
Applicant: Genentech, Inc. Agent for Applicant (if applicable):		
Date of Application: 4-30-13 Date of Receipt: 5-1-13 Date clock started after UN:		
PDUFA Goal Date: 10-31-13		Action Goal Date (if different):
Filing Date: 6-30-13		Date of Filing Meeting: 5-29-13
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Neoadjuvant treatment of breast cancer, in combination with trastuzumab and docetaxel for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?		X		
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic/EDR
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			PeRC Mtg 7-10-13
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>				
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>			X	
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined?			X	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			OSI 6-5-13
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):			X	
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 1-18-13	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):			X	
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 5-29-13

BLA/NDA/Supp #: sBLA 125409/51

PROPRIETARY NAME: Perjeta®

ESTABLISHED/PROPER NAME: pertuzumab

DOSAGE FORM/STRENGTH: Liquid single use vial/420 mg/14 mL

APPLICANT: Genentech, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Perjeta is indicated for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin, and cyclophosphamide (FEC) or carboplatin.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elleni Alebachew (covering for Amy Tilley)	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Laleh Amiri Kordestani Suparna Wedam (Safety)	Y
	TL:	Patricia Cortazar	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		

Clinical Pharmacology	Reviewer:	Pengfei Song	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Lijun Zhang	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers – Safety	Susan Jenney		
Other attendees	Robert Justice Amna Ibrahim Michel Wissing (contractor)		X X X

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: 9-12-13 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="margin-left: 20px;">If no, was a complete EA submitted?</p> <p style="margin-left: 20px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Division, Robert Justice, M.D. and/or Amna Ibrahim, M.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 7-17-13</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter: Sent 6-26-13

<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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

/s/

AMY R TILLEY
07/12/2013

ALICE KACUBA
07/12/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: BLA 125409/051

Application Type: Efficacy Supplement

Name of Drug: Perjeta® (pertuzumab) Liquid single use vial

Applicant: Genentech, Inc.

Submission Date: April 30, 2013

Receipt Date: May 1, 2013

1.0 Regulatory History and Applicant's Main Proposals

Perjeta® (pertuzumab) was approved on June 8, 2012 for use 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 their metastatic disease. On April 12, 2013, a prior approval supplemental biologics application (sBLA) was approved to include the confirmatory results of the second interim analysis of overall survival.

This supplemental BLA submission provides for the expanded use of pertuzumab to include the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2cm in diameter).

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

YES

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

YES

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

YES

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

YES

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

YES

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

Selected Requirements of Prescribing Information (SRPI)

8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

AMY R TILLEY
07/02/2013

ALICE KACUBA
07/02/2013

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: 6/6/2013

To: Ann Meeker-O'Connell, Acting Division Director, DGPCPC
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Through: Laleh Amiri-Kordestani, MD, Medical Officer, DOP1/OHOP
Suparna Wedam, MD, Medical Officer, DOP1/OHOP
Patricia Cortazar, MD, Team Leader, DOP1/OHOP

From: Amy Tilley, Regulatory Health Project Manager/DOP1

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: sBLA 125409\51
Applicant/ Applicant contact information (to include phone/email): Genentech, Inc. Josephine Ing
650-225-2330 ing.josephine@gene.com
Drug Proprietary Name: Pertuzumab
NME or Original BLA: No
Review Priority: Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

Proposed New Indication: Neoadjuvant treatment of breast cancer, in combination with trastuzumab and docetaxel for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin

PDUFA: October 31, 2013
Action Goal Date: After ODAC (September, 11 2013)
Inspection Summary Goal Date: Mid-September 2013

OSI/DGCPC Consult
version: 01/16/2013

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
116798 (Dr LUCA GIANNI, ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI, MILANO, Italy)	WO20697	28	High accrual
116801(Dr TADEUSZ PIENKOWSKI, CENTRUM ONKOLOGII - INST.IM. MARIII SKŁODOWSKIEJ-CURIE, WARSZAWA, Poland)	WO20697	28	High accrual
116814 (Dr ANA LLUCH HERNANDEZ , HOSPITAL CLINICO UNIVERSITARIO DE VALENCIA, VALENCIA , Spain)	WO20697	16	High accrual

III. Site Selection/Rationale

The data is gathered solely from foreign sites. We chose sites with high accrual rate.

International Inspections:

Reasons for inspections:

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites:

We have requested these sites for inspection (international) because of the following reasons:

- The data is gathered solely from foreign sites.
- The sites in Italy and Poland represent the first and second highest accruing sites overall, respectively.
- The priority is:

1	116798 (Dr LUCA GIANNI, ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI, MILANO, Italy)
2	116801(Dr TADEUSZ PIENKOWSKI, CENTRUM ONKOLOGII - INST.IM. MARIII SKŁODOWSKIEJ-CURIE, WARSZAWA, Poland)
3	116814 (Dr ANA LLUCH HERNANDEZ , HOSPITAL CLINICO UNIVERSITARIO DE VALENCIA, VALENCIA , Spain)

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DG CPC.

IV. Tables of Specific Data to be Verified (if applicable)

Not applicable.

Should you require any additional information, please contact Amy Tilley (RPM) at 301-796-3994 or Laleh Amiri (medical officer) at 301-796-7547.

Concurrence:

Patricia Cortazar, M.D. Medical Team Leader
Laleh Amiri-Kordestani, M.D. Medical Reviewer
Robert Justice, M.D. Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

AMY R TILLEY
06/06/2013

ROBERT L JUSTICE
06/06/2013