CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125427Orig1s000

<u>CHEMISTRY REVIEW(S)</u>

Food & Drug Administration

Memorandum

Date: February 21, 2013

From: Linda Ng, Ph.D.
Senior Policy Advisor,
New Drug Manufacturing Assessment Branch
Division of GMP Assessment
Office of Manufacturing & Product Quality, OC

Through: Tara Gooen
Acting Branch Chief, New Drug Manufacturing Assessment Branch
David Doleski, Division Director,
Division of GMP Assessment

Subject: BLA 125427, Kadclya (trastuzumab emtansine for injection) 100 mg/vial and 160 mg/vial, Genentech Manufacturing Facilities Assessment

To: The File

Genentech Inc. is the applicant for Kadclya [T-DM1] (trastuzumab emtansine for injection) 100 mg/vial and 160 mg/vial. The indication is for HER2 positive metastatic breast cancer. The PDUFA date is February 26, 2013.

The firms associated with the manufacture of T-DM1 are shown in Attachment A, Figure 1. The drug product is manufactured [redacted] (b) (4) During the inspection [redacted] (b) (4) it was discovered that investigations were initiated [redacted] (b) (4) The [redacted] (b) (4) are a CGMP concern. However, the concern was addressed through a post-marketing requirement (PMR) and post-marketing commitment. The purpose of this memo is to document the strategy that was taken to reach a solution.

An inspection of [redacted] (b) (4), drug substance manufacturer, [redacted] (b) (4), revealed [redacted] (b) (4). The investigators were Bo Chi and Maria Candau-Chacon from BMAB/OMPQ and Francisco Borrego from OBP.

A for-cause inspection [redacted] (b) (4) was performed [redacted] (b) (4) by Regina Brown, who is an investigator within OMPQ. [redacted] (b) (4) is the supplier of DM1 intermediate for the drug substance T-DM1. [redacted] (b) (4)

The other supplier of DM-1 is [redacted] (b) (4) and identified by FEI [redacted] (b) (4). Since this facility had already been inspected for manufacturing of drug substance within the prescribed timeframes, the acceptability of the firm was based on the profile. Therefore, there was not an inspection performed of this facility in conjunction with the review of this BLA.

An inspection of [redacted] (b) (4) FEI [redacted] (b) (4) was performed by BMAB - Michelle Clark-Stuart and Donald Obenhuber [redacted] (b) (4)

Genentech maintains responsibility for the contract manufacturing sites and has not authorized communication [redacted] (b) (4)

During the review and inspection of the manufacturing facilities, manufacturing quality issues were identified. In order to address the manufacturing quality issues, we determined that Genentech should initiate the following actions:

1. Perform a risk assessment of material compatibility at all stages of manufacturing and packaging of the drug substance and drug product.
2. Address the issue [redacted] (b) (4)

3. An [redacted] (b) (4) test with acceptance criterion should be included in the Acceptance Specification for DM1 [redacted] (b) (4) and Release Specification at the DM1 suppliers. This is to address the issue [redacted] (b) (4)
4. The [redacted] (b) (4) matter should be excluded. A test and acceptance criterion should be proposed at all three sites.

A number of comments [redacted] (b) (4) were generated prior to NDMAB involvement and sent in IR #7 dated October 23, 2012 to Genentech. The responses pertinent to the DM1 [redacted] (b) (4)/CGMP for the small molecule were covered in Anne Marie Russell/Xiao Chen's ONDQA review, pp. 36-41 dated January 29, 2013. However, the firm's response was limited [redacted] (b) (4) Further, the firm did not provide a root-cause analysis [redacted] (b) (4) However, the Sponsor indicated that they are initiating a comprehensive, formal root cause analysis to identify and confirm the origins [redacted] (b) (4) that have been identified to date and will work [redacted] (b) (4) to implement any additional CAPAs.

Based on the concerns [redacted] (b) (4), OMPQ initiated a for-cause inspection request [redacted] (b) (4) The resulting inspection [redacted] (b) (4) described two complaints dated [redacted] (b) (4) from Genentech related to [redacted] (b) (4) issues. During her inspection, Ms. Brown, described the root cause analysis [redacted] (b) (4) as listed. The items could contribute [redacted] (b) (4) to DM1 [redacted] (b) (4)

[redacted] (b) (4)

The following CAPAs [redacted] (b) (4) were initiated (b) (4) [redacted] in an attempt to improve quality for future DM1 intermediate:

[redacted] (b) (4)

These improvements have [redacted] (b) (4) observed in batches [redacted] (b) (4). Therefore, while there were quality problems with several DM-1 lots manufactured [redacted] (b) (4), we decided to further pursue the overall quality issues through the review process and the inspection follow-up process. .

On January 17, 2013, we sent a seven-item information request (IR #24). See Attachment B. Items 1 and 2 were drafted by ONDQA/NDMAB, and item 3 to 5 by NDMAB. Items 6 and 7 were review related from ONDQA. The first IR item pertained to an in-process [redacted] (b) (4) test [redacted] (b) (4) and release tests [redacted] (b) (4) at the DM-1 intermediate sites. The second IR item requested that the firm propose an in-process test with acceptance criterion (b) (4) [redacted] at the site of the TDM-1 manufacturing and a test [redacted] (b) (4) as part of the Release Specification at the DM1 facilities. Lastly, we requested that the firm describe the proposed plan with disposition of failed lots of DM1.

The three items drafted by NDMAB concerned the risk assessment for material compatibility at the DM-1 manufacturing sites, the [redacted] (b) (4) sterilization process [redacted] (b) (4), and the issue of whether the manfuacturing proces described in the BLA was consistent with the actual manufacturing process.

On January 25, 2013, Genentech responded to the questions in IR #24 including question #1 regarding the [redacted] (b) (4) test and question #2 regarding the [redacted] (b) (4) issue. For the [redacted] (b) (4) test, the firm's response was reviewed and found acceptable. This is also documented in the ONDQA CMC review dated January 29, 2013.

For the [redacted] (b) (4) issue, Genentech proposed to implement a test [redacted] (b) (4) [redacted] (b) (4) Due to the shortage of time, we decided to have Genentech address the issue by a PMR #2 involving a proposed mass test [redacted] (b) (4) for the entire batch. See Attachment C.

On January 31, 2013, a telecon was initated between the Agency and Genentech concerning the three proposed PMRs/PMC. Each PMRs/PMC was discussed in detail.

On February 1, 2013, [redacted] (b) (4) was contacted for follow up to their CAPAs with a list of questions as discussed in a teleconference call. The questions were uploaded in DARRTS in the communicated dated Feb. 6(See Attachment D). The responses summarized in email [redacted] (b) (4) dated February 11, 2013 (archived in FDA's MARCS-CMS) indicated that all except four of the items have been addressed. Three of the four will be addressed [redacted] (b) (4) and the last one will be addressed [redacted] (b) (4) See Attachment E.

On February 5, 2013, Genentech submitted an amendment in response to the January 31 telecon, with respect to the PMCs discussed on January 31. The amendment proposed that, effective immediately, the Sponsor will implement an interim Action Limit [redacted] (b) (4) Further, Genentech indicated that [redacted] (b) (4) will be investigated to facilitate identification, root cause analysis, and implementation of corrective actions, as appropriate. [redacted] (b) (4)
This satisfied the need for a more robust testing method [redacted] (b) (4) for DM-1 intermediate as described in the proposed PMR #2. However, the issue [redacted] (b) (4) had not been resolved as the related investigation was still incomplete.

On February 7, 2013, Genentech submitted an amendment [redacted] (b) (4)

Subsequently, on February 15, 2013, we sent a communication to Genentech requesting a PMR as follows:

> *Provide quarterly reports on the status of any* [redacted] (b) (4) *These reports should include, at a minimum, a summary of the root-cause analyses, associated corrective actions, and disposition of all affected DM1 batches. Also, provide the disposition of any potentially affected finished*

product batches using these affected DM1 batches. Submit an interim report documenting that the manufacturing processes have been appropriately controlled at the manufacturing facilities according to Genentech's evaluation. The interim report should include a request for follow-up inspection(s). Submit a final report with a statement concerning the follow-up performed on the [redacted] (b) (4) *issues during the course of the FDA inspection(s), an update on whether there have been any further instances of* [redacted] (b) (4)*, and a proposal to prevent* [redacted] (b) (4) *managed by each site's quality system.*

The reason for requesting this was to ensure that the investigation and corrective actions will be completed and reported to the Agency. This PMR was developed in association with the TB-EER, which contains a compliance recommendation on the facilities associated with the manufacturing of this product. Typically, [redacted] (b) (4) issue would be resolved prior to approval. However, for this particular product, the [redacted] (b) (4) tests at the three facilities together with the PMR mitigated the risk of potential [redacted] (b) (4) and allowed us to make a recommendation for approval.

In addition, a proposed PMC was sent to Genentech due to the fact that Genentech had not adequately addressed the issue [redacted] (b) (4) in the BLA. In the November 2, 2012 response, Genentech addressed the issue [redacted] (b) (4) However, during the inspection, it was revealed [redacted] (b) (4) Genentech has not yet addressed this issue. Further, the assessment from Genentech submitted in the November 2, 2012 amendment does not contain actual data [redacted] (b) (4) This response is unacceptable because it is based only on assumptions, rather than on data. Therefore, we requested the PMC as listed below:

Provide a material compatibility assessment [redacted] (b) (4) [redacted] (b) (4) *Provide a toxicological risk assessment* [redacted] (b) (4) *If significant* [redacted] (b) (4) *are identified during these assessments, initiate action to mitigate the source(s) of risk to product quality.*

Provided that Genentech agrees to the PMR and PMC listed above, then we agree that approval is warranted.

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/s/

LINDA L NG
02/21/2013
Tara Gooen concurs

JOSEPH D DOLESKI
02/22/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:
The review team should email this form to the email account “CDER-TB-EER” to submit:
1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[3] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: 2/27/13
Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): STN125427/0
Product(s): trastuzumab-MCC-DM1 (trastuzumab emtansine, T-DM1)

Short summary of application: New BLA

FACILITY INFORMATION

Manufacturing Location: Antibody intermediate manufacturing site
Firm Name: Genentech
Address: 1000 New Horizons Way
Vacaville, CA 94080
FEI: 3002902534
Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for Trastuzumab intermediate

Inspected by SAN-DO from 6/15/10-6/23/10 and classified NAI. This CGMP inspection found the CBI profile updated and acceptable. This site was found acceptable for manufacturing operations for Trastuzumab under BLA 103792. This site was also inspected by OMPQ/DGMPA/NDMAB from 3/20/12-3/28/12 and classified VAI for drug substance manufacturing operations.

Manufacturing Location: Antibody intermediate manufacturing site
Firm Name: Roche Singapore Technical Operations PTe. Ltd.
Address: Singapore 637394
FEI: 3007164129
Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for Trastuzumab intermediate

Inspected by IOG from 4/26/12-5/3/12 and classified VAI. This was a CGMP inspection that found the TRP profile was updated and found acceptable. This site was also found acceptable for manufacturing operations for Trastuzumab under BLA 103792.

Manufacturing Location: DM1 intermediate manufacturing site
Firm Name: [redacted] (b) (4)
Address: [redacted] (b) (4)

[redacted] (b) (4)

FEI: [redacted] (b) (4)

Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for DM1 intermediate

Inspected [redacted] (b) (4) and classified NAI. This CGMP inspection found the [redacted] (b) (4) profiles updated and acceptable. The manufacture of the DM1 intermediate is considered [redacted] (b) (4); therefore the current compliance history at the time of the initial TB-EER was relevant for this facility in support of this BLA.

Due to evidence of [redacted] (b) (4) DM1 lots observed during the inspection (b) (4) [redacted] a for-cause inspection was conducted by OMPQ/DIDQ [redacted] (b) (4). This inspection covered [redacted] (b) (4) issues and was initially classified VAI. The firm's formal response and follow up discussions with Genentech [redacted] (b) (4) were initially inadequate. As a result an IR letter [redacted] (b) (4) was sent to the sponsor on 10/23/12. Genentech's IR response of 11/2/12 and the information subsequently provided during the 1/31/13 teleconference have been considered by NDMAB and found to not adequately address the issues. Therefore, Genentech has made commitments to address these issues subsequent to approval via a PMR. For additional information, please see the primary review of 2/12/13 by Xiao Chen, ONDQA, available in DARRTS.

As commitments [redacted] (b) (4) have been agreed to by the sponsor and included in the action letter, this site is considered acceptable for the manufacture of the DM1 intermediate for this BLA.

Manufacturing Location: DM1 intermediate manufacturing site

Firm Name: [redacted] (b) (4)

Address: [redacted] (b) (4)

FEI: [redacted] (b) (4)

Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for DM1 intermediate

Inspected [redacted] (b) (4) and classified VAI. This CGMP inspection found the [redacted] (b) (4) profile updated and acceptable. The manufacture of the DM1 intermediate is considered [redacted] (b) (4); therefore the current compliance history is adequate to provide an acceptable recommendation for this facility in support of this BLA.

Due to evidence of [redacted] (b) (4) DM1 lots observed during the inspection (b) (4) [redacted], commitments [redacted] (b) (4) have been included in the action letter. Though the compliance history is slightly out of date, the compliance history window can be extended for the purposes of this BLA as the profile is only out of date by 1 month. This site is considered acceptable for the purposes of this BLA.

Manufacturing Location: Testing site

Firm Name: [redacted] (b) (4)

Address: [redacted] (b) (4)

FEI: [redacted] (b) (4)

Short summary of manufacturing activities performed: [redacted] (b) (4) Testing

Inspected [redacted] (b) (4) and classified NAI. This inspection covered control testing operations which included [redacted] (b) (4) testing. The CTL profile was updated and found acceptable.

Manufacturing Location: Drug substance manufacturing site
Firm Name: [redacted] (b) (4)
Address: [redacted] (b) (4)

FEI: [redacted] (b) (4)
Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for drug substance and drug product

Inspected by CDER-DMPQ [redacted] (b) (4) and classified VAI. This comprehensive pre-approval inspection found drug substance manufacturing operations acceptable for another BLA and the BTP profile was determined to be acceptable. Due to the complexity of the drug substance manufacturing and linking operations, BMAB inspected this facility in support of this BLA [redacted] (b) (4) and the inspection was classified VAI.

This Pre-license inspection covered manufacturing operations for this BLA and identified [redacted] (b) (4) in various DM1 lots. However, [redacted] (b) (4) quality system response to these issues was deemed adequate [redacted] (b) (4) The firm's formal response to observed deficiencies was reviewed by DIDQ and found adequate. As a result of these observations, a for-cause inspection was initiated [redacted] (b) (4) (see above). Commitments [redacted] (b) (4) have been included in the action letter. This site is considered acceptable.

Manufacturing Location: Drug product manufacturing site
Firm Name: [redacted] (b) (4)
Address: [redacted] (b) (4)

FEI: [redacted] (b) (4)
Short summary of manufacturing activities performed: Manufacture of DP, sterility and endotoxin testing for lot release

Inspected [redacted] (b) (4) and classified VAI. This was a CGMP inspection that provided coverage for sterile operations, including manufacturing [redacted] (b) (4) The SVS profile was updated and found acceptable.

Inspected by OMPQ/DGMPA/BMAB [redacted] (b) (4) and classified VAI. The firm's formal response to the observed deviations was found adequate. Subsequent information regarding practices at [redacted] (b) (4) resulted in concerns with the firm's practice [redacted] (b) (4) used for manufacture of this product. Genentech has made commitments on behalf of [redacted] (b) (4) to perform studies to demonstrate [redacted] (b) (4) during the manufacturing process. These commitments have been incorporated into the approval letter. This site is considered acceptable for the purposes of this BLA.

Manufacturing Location: DP packaging
Firm Name: Genentech
Address: 4625 Brookwood Parkway
Hillsboro, OR 97124

FEI: 3007232634
Short summary of manufacturing activities performed: Labeling and packaging

Inspected by CDER-OMPQ from 6/19/12-6/27/12 and classified VAI. This inspection provided coverage to packaging and labeling operations and found them acceptable.

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities: DP stability Container Closure Integrity Test

Inspected (b) (4) and classified NAI. This CGMP inspection covered testing operations and found them initially acceptable.

OVERALL RECOMMENDATION:

Review (b) (4):

For a review of CGMP issues associated with the 11/2/12 IR response, please see the primary review of 2/12/13 by Xiao Chen, ONDQA, available in DARRTS. This review was cleared through Linda Ng, OMPQ/DGMPA/NDMAB and documents NDMAB's review of (b) (4) concerns highlighted in IR responses.

NDMAB has evaluated (b) (4) concerns through inspectional coverage and follow up discussions with the sponsor and CMO's (IR and teleconference). During these discussions, Genentech's initial responses, investigations into the source (b) (4), and proposals (b) (4) were inadequate. The Agency determined that incorporating pre-marketing requirements and commitments into the action letter would generate adequate control (b) (4). These PMRs/PMCs (b) (4) have been drafted for inclusion in the action letter and have been agreed to by the sponsor.

As a result of these committments, NDMAB is able to make a recommendation that the manufacturing facilities for DM1 should be considered acceptable provided that Genentech and (b) (4) continue to address issues (b) (4) in DM1 lots.

OMPQ/DGMPA/NDMAB recommendation:

After evaluation of the inspections in support of this supplement and Genentech's concurrence with the PMRs/PMCs proposed by the Agency, there are no pending or ongoing compliance actions that prevent approval of this BLA.

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

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/s/

MAHESH R RAMANADHAM
02/20/2013

Memorandum

To: BLA 125427

Through: Linda Ng, Ph.D. (OMPQ) and Ali H Al Hakim, Ph.D.(ONDQA)

From: Xiao Hong Chen, Ph.D.

Date: 2/12/2013

Re: BLA 125427, Kadcyla (trastuzumab emtansine) for Injection
100 mg and 160 mg vials

BLA 125427 was submitted on August 27, 2012. The CMC review for the BLA and the amendments were completed and entered into Darrts on January 29, 2013. The CMC review recommended approval for the application from the ONDQA perspective.

CMC Review of the BLA consists of reviews from the three review teams, OBP (lead), ONDQA (small molecule drug/linker), and BMAB (Biotech Manufacturing Assessment Branch). Later in the review cycle, NDMAB (New Drug Manufacturing Assessment Branch) became involved in evaluating the GMP-related [redacted] issue. A for-cause inspection was carried out at the [redacted] facility that synthesizes DM1, the intermediate for the drug substance. After completing the CMC review in Darrts, several additional CMC-related PMRs/PMCs were proposed by the Agency after reviewing the response to IR#24. The PMR and PMC are accepted by the applicant, Genentech. These along with several previous PMRs/PMCs are summarized below. Note that PMRs/PMCs from BMAB are not captured in this review.

PMR/PMCs from OBP:

1. *PMR: Perform a multivariate characterization study to support the implementation* [redacted] *of SMCC* [redacted] *during manufacture of T-DM1 (Protocol submission: 31-Mar-2013; Study completion: 30- September-2013; Final report submission: 31-December-2013).*

2. *PMC: To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ado-trastuzumab emtansine, including procedures for accurate detection of neutralizing antibodies to ado-trastuzumab emtansine in the presence of ado-trastuzuamb emtansine levels that are expected to be present in the*

serum or plasma at the time of patient sampling. Final Report Submission (Assay and Methodology) Date: 30-Jun-2015

3. *PMC: To reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through Feb 28, 2014. Submit the Final Report as a Changes Being Effected-30 Supplement (CBE-30). Final Report Submission: 30-May-2014*

PMR from ONDQA:

4. *To develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data. The final report will be submitted as a Prior Approval Supplement (PAS).*
   Final Protocol Submission: 31-May-2013
   Study/Trial Completion: 31-December-2013
   Final Report Submission: 31-January-2013

PMR/PMCs from NDMAB:

5. *PMR:* Provide quarterly reports on the status of any [redacted] (b) (4) These reports should include, at a minimum, a summary of the root cause analyses, associated corrective actions, and disposition of all affected DM1 batches. Also, provide the disposition of any potentially affected finished product batches using these affected DM1 batches. Submit an interim report documenting that the manufacturing processes have been appropriately controlled at the manufacturing facilities according to Genentech's evaluation. The interim report should include a request for follow up inspection(s). Submit a final report containing the associated establishment inspection reports (EIR) and a proposal to prevent [redacted] (b) (4) managed by the site's quality system. *Final report submission: 30-July-2015.*

6. *PMC: Provide an assessment* [redacted] (b) (4) *Provide a toxicological risk assessment* [redacted] (b) (4)

> [redacted] (b) (4) *If significant* [redacted] (b) (4) *are identified during these assessments, initiate action to mitigate the source(s) of risk to product quality. Final report submission: 30-Jun-2013.*

The PMR/PMC #1 to #4 have been finalized and accepted by Genentech. Regarding the background information for PMR/PMC #1 to #4, refer to ONDQA CMC review and OBP review dated on January 29, 2013.

The PMR/PMC #5 and #6 are due to the [redacted] (b) (4) issues observed during the FDA pre-approval inspection [redacted] (b) (4) performed by BMAB reviewers. Following the discovery [redacted] (b) (4), the Agency has communicated with Genentech in multiple IRs and teleconferences in an effort to understand the root causes, evaluating the proposed controls and the impact on the finished product. [redacted] (b) (4) Since the [redacted] (b) (4) at DM1 manufacturing facility has been determined as a GMP issue, NDMAB has been consulted to take the lead on assessing this issue. A for-cause inspection [redacted] (b) (4) was conducted by Regina Brown from NDMAB [redacted] (b) (4), and the recommendation from the inspection is "Acceptable". In an effort to resolve [redacted] (b) (4) in future batches, test and acceptance criteria [redacted] (b) (4) were drafted by ONDQA and NDMAB. The ideal situation is to have [redacted] (b) (4) The PMR/PMC #5 and #6 proposed by NDMAB were discussed with Genentech in a teleconference on January 31, 2012.

In response to the PMR/PMC #5 and #6, Genentech has submitted an updated section for 3.2.S.2.2 Control of Critical Steps and Intermediates [Trastuzumab Emtansine]. The updated information in 3.2.S.2.2 includes of an in-process testing [redacted] (b) (4) If the action limit for the test is exceeded, a quality investigation will be conducted, including a root-cause analysis to understand the likely source(s) and mechanism(s) [redacted] (b) (4) Based on the outcome of the investigation, corrective actions will be implemented to prevent the reoccurrence in future batches. Any [redacted] (b) (4) will not be used for manufacturing trastuzumab emtansine. The proposed test and acceptance limit is found acceptable by both NDMAB and ONDQA.

The updated section for 3.2.S.2.2 also includes an in-process test [redacted] (b) (4) Review of this test was performed in ONDQA CMC review for this BLA dated January 29, 2013 entered in Darrts. It was found acceptable.

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/s/

XIAO H CHEN
02/12/2013

LINDA L NG
02/12/2013

ALI H AL HAKIM
02/12/2013

MEMORANDUM

Center for Drug Evaluation and Research - Food & Drug Administration
Division of Monoclonal Antibodies – HFD-123
NIH Campus, Bldg. 29B, Rm. 4E04, 29B Lincoln Drive, Bethesda, MD 20892
Telephone (301) 827-0830- Facsimile (301) 827-0852 - E-mail linan.ha@fda.hhs.gov

Date: February 6, 2013

From: Linan Ha, Ph.D., Product Reviewer, DMA/OBP

Through: Wendy Weinberg, Ph.D., Chief, LMO/DMA/OBP
Kathleen Clouse, Ph.D., Director, DMA/OBP

To: File STN125427 (License 1048)

Product: Ado-trastuzumab emtansine is an antibody-drug conjugate in which the humanized anti-HER2 IgG1, trastuzumab, is linked to the microtubule-inhibitory maytansinoid, DM1, via a thioether bond using the linker SMCC.

Indication: Patients with HER2-positive, (b) (4) metastatic breast cancer who have received previous treatment with trastuzumab and a taxane.

Sponsor: Genentech, Inc.

Contact: Ahmed Bassyouni
Phone: (650) 467-3951
Email: bassyouni.ahmed@gene.com

Purpose of submission: To finalize PMCs and to update the BLA with a revised post-approval stability program for ado-trastuzumab emtansine drug substance.

Summary: The purpose of this amendment is to update the BLA with two finalized PMCs and to finalize an outstanding information request to implement accelerated stability study as part of post approval stability protocol for ado-trastuzumab emtansine drug substance. Both were pending prior to the cGRMP deadline for primary review.

I. **The finalized PMCs are summarized below:**

1. *To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ado-trastuzumab emtansine, including procedures for accurate detection of neutralizing antibodies to ado-trastuzumab emtansine in the presence of ado-trastuzuamb emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling.*

   Final Report Submission (Assay and Methodology) Date: 06/30/2015

   The sponsor committed to applying the validated neutralizing assay to analyze positive samples from the planned phase III early breast cancer studies, [redacted] (b) (4)

   The proposed milestone for this PMC and the sponsor's response are deemed acceptable.

2. *To reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through Feb 28, 2014. Submit the Final Report as a Changes Being Effected-30 Supplement (CBE-30).*

   Final Report Submission: 05/31/2014

   The proposed milestone for this PMC is deemed acceptable.

II. Follow-up to IR issued on January 30, 2013: modification of post-approval stability protocol for ado-trastuzumab drug substance to implement accelerated stability testing.

The following response was received on January 31, 2013: The updated post approval stability protocol for ado-trastuzumab emtansine drug substance includes a protocol for accelerated testing [redacted] (b) (4) [redacted] The updated post approval stability protocol has been implemented to the related BLA section and is summarized in the following tables, excerpted from the submission.

Table 1 Post-Approval Stability Protocol for Trastuzumab Emtansine Drug Substance Annual Batches, Study Condition: [redacted] (b) (4)

(b) (4)

[redacted]

Table 2 Post-Approval Stability Protocol for Trastuzumab Emtansine Drug Substance Annual Batches, Study Condition: [redacted] (b) (4)

(b) (4)

[redacted]

The proposed post approval stability protocol for ado-trastuzumab emtansine drug substance is deemed acceptable.

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/s/

LINAN HA
02/07/2013

WENDY C WEINBERG
02/07/2013

KATHLEEN A CLOUSE STREBEL
02/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date:	29 January 2013
To:	Administrative File, STN 125427/0
From:	Reyes Candau-Chacon, Ph.D., Reviewer, OC/OMPQ/DGMPA/BMAB
Through:	Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject:	New Biologic License Application (BLA)
US License:	1048
Applicant:	Genentech, Inc.
Facilities:	[redacted] (b) (4) (FEI # [redacted] (b) (4))
Product:	KADCYLA™ (ado-trastuzumab emtansine)
Dosage:	Lyophilized cake (100 mg/vial and 160 mg/vial) for reconstitution with sterile WFI to a final concentration of 20 mg/mL (5.0 mL and 8.0 mL) to be delivered by infusion
Indication:	Treatment of patients with HER2-positive [redacted] (b) (4) metastatic breast cancer which have received prior treatment with trastuzumab and a taxane
Due date:	26 February 2013

<u>Recommendation for Approvability</u>: The Drug Product Section for BLA 125427 was reviewed and is recommended for approval from a CMC sterility assurance and microbiology product quality perspective with the following post-marketing commitments:

1. Transfer the methodology for validated dye ingress testing developed by Genentech to [redacted] (b) (4). Confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method by February 28, 2013 and report changes to the Agency in the 2014 Annual Report.
2. Conduct controlled studies to assess the risk of endotoxin masking [redacted] (b) (4) using endotoxin spiked trastuzumab emtansine drug product [redacted] (b) (4) and submit results and updated specifications to the Agency by March 29, 2013 as a PAS.
3. If endotoxin masking is observed in the drug product [redacted] (b) (4), develop an alternative method to quantitate endotoxin in the finished trastuzumab emtansine drug product [redacted] (b) (4) using routine production conditions. Any change in the analytical methods should be approved by the Agency before implementation. Submit protocol to the Agency by September 30, 2013 as a PAS.
4. Dedicate [redacted] (b) (4) for trastuzumab emtansine DP manufacture and submit results from sterilization validation and 3 media fill simulations to the Agency by June 30, 2013 as a CBE-0.

5. Conduct cleaning verification [redacted] (b) (4) [redacted] and report the updated [redacted] (b) (4) procedures to the Agency in the 2014 Annual Report.

Review Summary

Genentech, Inc. has submitted BLA 125427 to license trastuzumab emtansine and the associated drug substance and drug product manufacturing processes. Trastuzumab emtansine is an antibody-drug conjugate (ADC), comprised of a monoclonal antibody (trastuzumab) and a chemotherapy agent (DM1) attached by a stable linker. Trastuzumab emtansine is designed to target and inhibit HER2 signaling and to deliver the chemotherapy agent inside HER2-positive cancer cells. Trastuzumab emtansine drug product is presented as a lyophilized cake for reconstitution in glass vials (100 mg/vial and 160 mg/vial).

BLA 125427 was submitted in eCTD as a rolling BLA. Module 3 of the application was included in amendment 0003, submitted on August 1, 2012. This review contains the assessment of the manufacturing process of trastuzumab emtansine drug product form a sterility assurance and microbiology product quality perspective. The drug substance review is covered in a separate product quality microbiology review.

Amendments Reviewed for Drug Product Quality Microbiology

Information Request date	Question numbers	Amendment sequence	Amendment date
24-Sep-2012	all	0019	9-Oct-2012
22-Oct-2012 17-Nov-2012 (clarification)	8	0038 n.a. (e-mail)	5-Nov-2012 13-Nov-2012
8-Nov-2012 20-Nov-2012 (clarification)	all	0052 e-mail 0070	20-Nov-2012 20-Dec-2012 21-Dec-2012
30-Nov-2012	all	0062	7-Dec-2012
		n.a. (e-mail)	20-Dec-2012
		0088	28-Jan-2013
14-Dec-2012	all	0069	21-Dec-2012
14-Jan-2013 (T-con.)			
16-Jan-2013	1-5	0078	18-Jan-2013
18-Jan-2013	all	0081	23-Jan-2013
18-Jan-2013 (T-con.)			
23-Jan-2013	all	0087	24-Jan-2013

25-Jan-2013	all	0091	28-Jan-2013

Consults for Drug Product Quality Microbiology

Consult date	Type	Division	Response
15-Jan-2013	Toxicology	OND DOP1	15-Jan-2013
23-Jan-2013	Toxicology	OND DOP1	23-Jan-2013
24-Jan-2013	Toxicology	OND DOP1	24-Jan-2013
24-Jan-2013	Toxicology	OND DOP1	24-Jan-2013
25-Jan-2013	CMC briefing to the Center Director		

Toxicology consults are reviewed in the Pharm/Tox team leader memo (Todd Palmby).

<u>Review Narrative</u>

1.14 LABELING

1.14.1 Draft labeling

Your package insert text (Section 16.2) contains the following information:

(b) (4)

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

/s/

REYES CANDAU-CHACON
01/29/2013

PATRICIA F HUGHES TROOST
01/29/2013

BLA 125-427

KADCYLA™ (trastuzumab emtansine) for Injection

Genentech, Inc.

Xiao-Hong Chen, Ph.D.
(T-DM1 drug substance and drug product)
&
Anne Marie Russell, Ph.D.
(DM1 intermediate and SMCC linker)

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I

CMC Review of BLA 125-427

For the Division of Oncology Products 1 (DOP1)

Table of Contents

Chemistry Review Data Sheet

1. BLA 125-427

2. REVIEW #1

3. REVIEW DATE: 28-January-2013

4. REVIEWERS: Xiao-Hong Chen, Ph.D (drug substance, drug product)
   Anne Marie Russell, Ph.D (drug substance intermediate, linker)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 71,072	16-DEC-2005

6. SUBMISSION(S) BEING REVIEWED:

For review of T-DM1 drug substance and product (Dr. Chen)			
Submission Reviewed		**Receipt Date**	
Original		27-AUG-2012	
Amendment		17-OCT-2012	Response to IR for questions regarding S.2.6
Amendment		02-NOV-2012	Response to IR#7
Amendment		02-Nov-2012	Response to IR#8
Amendment		07-Dec-2012	Response to IR#16
Amendment		07-Dec-2012	Response to IR#19
Amendment		28-Jan-2013	Response to IR#24 (Q1 and 2)
Amendment		29-Jan-2013	Updated specifiocation table for drug product
For review of DM1 intermediate and SCCM linker (Dr. Russell)			
Submission Reviewed	**EDR Seq #**	**Receipt Date**	**Comment**
Original	003	01-Aug-2012	Rolling Review CMC module
Amendment	031	31-Oct-2012	Response to IR#6
Amendment	034	02-Nov-2012	Meeting request: (b) (4) specifications
Amendment	049	15-Nov-2012	Response to IR#12 (Meeting Request)
Amendment	055	03-Dec-2012	Partial Response to IR#15
Amendment	058	07-Dec-2012	Partial response to IR#15 (remainder)
Amendment	065	14-Dec-2013	Update sections of application affected by Response to IR#6 and IR#15
Amendment	071	03-Jan02013	Correction to Response to IR#15
Amendment	Email	25-Jan-2013	Partial response to IR#24 (Q6)
Amendment	email	28-Jan-2013	Partial response to IR#24 (Q1,2,7)
Amendment	email	29-Jan-2013	Updated analytical procedures and specifications for DM1

7. NAME & ADDRESS OF APPLICANT:

Name:	Genentech, Inc.
Address:	1 DNA Way South San Francisco, CA 94080-4990
Representative:	Erica J. Evans, Ph.D. Regulatory Program Management
Telephone:	650-467-2157

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Kadcyla™
b) Non-Proprietary Name (USAN): trastuzumab emtansine
c) Chemical Name: trastuzumab-MCC-DM1
Code Name/#: T-DM1
Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: BLA, 21 CFR Part 601

10. PHARMACOL. CATEGORY: Single agent for treatment of patients with HER2-Positive Metastatic Breast Cancer

11. DOSAGE FORM: For Injection, Lyophilized cake

12. STRENGTH/POTENCY: 100 mg and 160 mg vials

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. <u>SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):</u>

__X__ SPOTS product – Form Completed

_____ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Theoretical Molecular Mass	148,781 Da (protein mass 145,423 + [957.5 linker-drug mass × 3.5])
Ratio DM1/Trastuzumab	3.5 (average) [redacted] (b) (4)
Glycosylation	[redacted] (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	71,072	Genentech	Initial IND submission on 12/19/2005

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULT	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Correlation between DAR and drug load distribution/unconjugated antibody content	November 15, 2012	Review completed by Dr. Meiyu Shen on 12-Dec-2012.	The correlation between DAR and drug load distribution/unconjugated antibody content (b) (4) [redacted] Recommended the sponsor measure free antibody content (b) (4) [redacted]
EES	N/A			
Pharm/Tox	Qualification (b) (4) [redacted] in the drug product	Oct 23, 2012	Nov 27, 2012	Informal email consult regarding the qualification (b) (4) [redacted] in the T-DM1 drug substance and drug product.
Pharm/Tox	DM1 impurity acceptance criteria		Jan 23, 2013	Informal email consult regarding the acceptability of DM1 impurity criteria justified by clinical experience
Biopharm	N/A			
ODS/DMEPA	N/A			
Methods Validation	N/A			
EA	N/A			
Microbiology	N/A			

The Chemistry Review for BLA 125-427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the small molecule DM1 perspective, this BLA is recommended for approval based on the adequate CMC information provided in the BLA and the post-marketing requirement Genentech has agreed upon (see below).

B. Recommendation on Post Marketing Requirements, Post Marketing Commmitments, Agreements, and/or Risk Management Steps, if Approvable

To develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data. The final report will be submitted as a Prior Approval Supplement (PAS).

Final Protocol Submission: 31-May-2013
Study/Trial Completion: 31-December-2013
Final Report Submission: 31-January-2013

II. Summary of Chemistry Assessment

<u>Regulatory Background</u>

The initial IND for T-DM1 was submitted on December 19, 2005. Throughout the drug development program, several major industrial meetings were held to discuss the pertinent CMC issues, which include pre IND meeting dated March 14, 2005, two Type C meetings held on July 7, 2009 and March 11, 2010. The BLA 125427 for KADCYLA™ (trastuzumab emtansine) for injection was submitted on August 27, 2012 per 21 CFR Part 601, and the application was filed on October 28, 2012, with a priority review clock of six month. PDUFA date for the BLA is February 27, 2013.

The quality review team for the BLA consists of OBP (responsible for antibody and overall submission lead), ONDQA (responsible for small drug, linker, and the conjugation process) and BMAB (responsible for product microbiology and pre-approval inspection). Later in the review, OMPQ also is involved [redacted] (b) (4)

A. Description of the Drug Product(s) and Drug Substance(s)

Trastuzumab emtansine (also known as T-DM1) is a novel HER2-targeted antibody-drug conjugate (ADC) which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). T-DM1 is a heterogeneous mixture, with respect to drug conjugation ratio and also with respect to the variety of post-translational modifications of the antibody. The average antibody to drug ratio (ADR) is [redacted] (b) (4), with a distribution between zero and eight MCC-DM1 molecules per antibody. Hence, the calculated molecular formula (148,781 Da) and predicted average molar mass of T-DM1 are based on the average molar mass of Trastuzumab and assume an average of 3.5 drug-linkers conjugated per antibody.

<u>T-DM1 Drug Substance</u>

T-DM1 bulk drug substance is manufactured [redacted] (b) (4) by a contract manufacturer, [redacted] (b) (4) Trastuzumab emtansine is an antibody-drug conjugate produced from two intermediates, the monoclonal antibody trastuzumab and the cytotoxic agent maytansinoid DM1, which are linked together using the heterobifunctional linker SMCC, [redacted] (b) (4)

The manufacturing process starts with [redacted] (b) (4)

Through the process characterization studies and manufacturing process validation studies, Genentech has identified critical steps and CPPs in step of the manufacturing process. Using both univariate and multivariate process characterization studies, Genentech has defined PARs and MARs [redacted] (b) (4) The MARs will be the normal manufacturing operating ranges. The completed validation studies have used both [redacted] (b) (4) DM1 batches to produce 6 registration batches (3 registration batches from each suppliers of DM1).

DM1 is the small drug, isolated intermediate in the manufacturing of trastuzumab emtansine (T-DM1) drug substance. It is manufactured [redacted] (b) (4) at two contract specialty manufacturing sites [redacted] (b) (4) Specifications and retest periods have been established for the intermediate and starting materials.

SMCC is the small drug linker in the manufacturing of trastuzumab emtansine (T-DM1) drug substance. It is commercially available, [redacted] and controlled by specifications.

CMC information for trastuzumab antibody is reviewed by Dr. Linan Ha from OBP.

Structural characterization of T-DM1 has been conducted using a variety of, immunochemical, biochemical, spectroscopic, and analytical techniques. The data confirm that T-DM1 conjugation site is at the side chain of the amino acid lysine residue. Drug load distribution studies were conducted using MS analysis, demonstrating a mixture of drug-loaded species containing between zero and eight DM1 molecules per antibody that predominantly contains 2 to 4 drugs per antibody [redacted] RP-HPLC in combination with MS was used to identify and quantify [redacted] in the product [redacted]

Batch analysis data for all clinical batches (11 Phase I batch, 28 Phase II batches and 32 Phase III and registration batches) were submitted for review. Drug substance specifications were established based on the controls used throughout the development. The acceptance criteria were proposed based on the analytical results of 32 Phase III/3 registration batches. Genentech did not have appropriate test to control the unconjugated antibody content. Based on the Agency's comment Genentech has agreed to develop, validate and implement the iCIEF method to control the unconjugated antibody content in the drug substance and drug product post approval. A PMR has been conveyed to Genentech, and it has a timeline to finish the study by December 2013.

The bulk drug substance is formulated with all excipients in the drug product and it is stored [redacted] Stability data for the bulk drug substance demonstrated that it is stable when stored at the long term storage condition [redacted] A [redacted] retest can be granted for trastuzumab emtansine stored [redacted]

<u>T-DM1 Drug Product</u>
KADCYLA (trastuzumab emtansine) for Injection single-use vial is provided as a lyophilized formulation, with two presentations, 100 mg (in 15 mL Type I vial) and 160 mg (in 20 mL Type I vial) vials. Trastuzumab emtansine vial upon reconstitution yields a solution containing 20 mg/mL trastuzumab emtansine, 10 mM sodium succinate, 6% w/v sucrose, and 0.02% w/v polysorbate 20, pH 5.0. The two configurations are dose proportional [redacted] The reconstituted drug product is diluted in 0.9% saline [redacted] prior to IV infusion.

As the drug substance is a formulated bulk drug product that contains all excipients, the drug product manufacturing consists of sterile [redacted] (b) (4) lyophilization, and packaging. The controls of the drug product [redacted] (b) (4) are included, and some acceptance criteria are [redacted] (b) (4) of the drug substance.

Up to 36 months long term stability data (24 months of data for the 100 mg configuration and 36 months of data for the 160 mg configuration) are provided along with 6 months of accelerated stability data to support the shelf life of the drug product. Based on the data, a 36-month expiry for 160 mg configuration and a 24-month expiry for 100 mg configuration can be granted for the drug product stored at 2-8°C.

B. Description of How the Drug Product is Intended to be Used

KADCYLA (trastuzumab emtansine) for Injection is a HER2-directed antibody-drug conjugate indicated for treatment of patients with HER2-positive metastatic breast cancer.

The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The vial containing 100 mg or 160 mg of trastuzumab emtansine is reconstituted with 5 mL or 8 mL Sterile Water for Injection, USP, respectively, to yield a 20 mg/mL trastuzumab emtansine solution. Based on the dose the required amount of the reconstituted solution, is further diluted in 0.9% saline [redacted] (b) (4) to achieve an infusion solution of [redacted] (b) (4) trastuzumab emtansine, which should be used for IV infusion with a 2 μ in-line filter within 4 hours of vial reconstitution.

C. Basis for Approvability or Not-Approval Recommendation

Based on the CMC information submitted, this BLA is recommended for approval. There are no outstanding CMC deficiencies from the small molecule (CMC) perspective. A PMR to develop and validate an iCIEF method to be used as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data is recommended and accepted by Genentech.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao-Hong Chen, Ph.D. and Anne Marie Russell, Ph.D.
Branch Chief Name/Date: Ali Al Hakim, Ph.D.

C. CC Block

Lisa Skarupa/OHOP/DDOP/Regulatory PM
Haripada Sarker/ONDQA/CMC Lead
Anne Marie Russell/ONDQA/CMC Reviewer
Sarah Pope Miksinski/ONDQA/DNDQA I/Acting Director

Joe Welch/OBP/PM
Linan Ha/OBP/Product Reviewer
Wendy Weinberg/OBP/Team Leader

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/s/

ANNE M RUSSELL
01/29/2013

XIAO H CHEN
01/29/2013

ALI H AL HAKIM
01/29/2013
I concur with the recommendation.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

The Quality Team Leader's Executive Summary

From: Wendy C. Weinberg, Ph.D.
Division of Monoclonal Antibodies (DMA)

Through: Kathleen A. Clouse, Ph.D., Director
Division of Monoclonal Antibodies

BLA Number: 125427
Product: Ado-trastuzumab emtansine (KADCYLA)
Sponsor: Genentech, Inc.

Date of Review: January 24, 2013
Due Date of CDTL Memo: February 5, 2013
PDUFA Date: February 26, 2013

INDEX

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125427 for KADCYLA (Ado-trastuzumab emtansine) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of KADCYLA (Ado-trastuzumab emtansine) is well controlled, and leads to a product that is pure and potent. The conditions used in manufacturing have been sufficiently validated and a consistent product was produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.

II. APPROVAL LETTER INFORMATION

The following information should be provided to the sponsor in an approval letter:

Under this license, you are approved to manufacture ado-trastuzumab emtansine bulk drug substance [redacted] (b) (4) and ado-trastuzumab emtansine final drug product [redacted] (b) (4) Drug product labeling and packaging will be done at Genentech Hillsboro Fill Finish Facility in Hillsboro, OR.

The trade name for ado-trastuzumab emtansine is KADCYLA.

The expiration date for ado-trastuzumab emtansine drug product, 160mg/vial, shall be 36 months at 2-8°C. The expiration date for ado-trastuzumab emtansine drug product, 100mg/vial, will be 24 months at 2-8°C.

The expiration date for ado-trastuzumab emtansine drug substance shall be [redacted] (b) (4) A cumulative expiry study supported holding drug substance [redacted] (b) (4)

The expiration date for trastuzumab intermediate is [redacted] (b) (4)

We have approved the stability protocols in your license application for the purpose of [redacted] (b) (4) the expiration dating period of the drug substance and drug product under 21 CFR 601.12. Data supporting [redacted] (b) (4) the expiration dating period should be submitted to the BLA Annual Report.

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

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

The following post-marketing requirements from DMA have been conveyed to Genentech:

PMR1:
Perform a multivariate characterization study to support the implementation [redacted] (b) (4) of SMCC [redacted] (b) (4) during manufacture of ado-trastuzumab emtansine.
Final Protocol submission: March 31, 2013
Study completion: September 30, 2013
Final report submission: December 31, 2013

PMC1:
Develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ado-trastuzumab emtansine, including procedures for accurate detection of neutralizing antibodies to ado-trastuzumab emtansine in the presence of ado-trastuzumab emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling.
Note: It was requested that the timing of PMC#2 be coordinated with the clinical trial timeline(s), such that the PMC is satisfied by the time the clinical samples are to be analyzed using these methods.
Note: This PMC and milestone dates were still pending at the time of the GRMP deadline for the TL Executive Summary.

PMC2:
Reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through February, 2014. The final report will be submitted as a CBE30.
Note: This PMC and milestone dates were still pending at the time of the GRMP deadline for the TL Executive Summary.

Following discussions between DMA and ONDQA reviewers, the following PMR from ONDQA was conveyed to the sponsor:

To develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data. The final report will be submitted as a Prior Approval Supplement (PAS).
Final Protocol submission: May 31, 2013
Study completion: December 31, 2013
Final report submission: January 31, 2014

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

Refer to the list of PMRs/PMCs in section III to address any outstanding deficiencies from a DMA product quality perspective.

Note: There were significant CMC concerns related to manufacture of ado-trastuzumab emtansine, both from the small molecule (DM1) and CGMP perspective. The small molecule concern relates to [redacted] (b) (4) ***This was identified upon inspection of the*** [redacted] (b) (4) ***drug substance manufacturing facility and brought back to the Agency as a review issue. Refer to reviews from ONDQA and NDMAB regarding this issue. Significant CGMP concerns include: 1) endotoxin masking effects and lack of a validated test method to measure endotoxin in final drug product stored in glass vials; 2) inadequate cleaning validation*** [redacted] (b) (4) ***at the drug product facility*** (b) (4) [redacted] ***Refer to reviews from BMAB regarding these CGMP issues.***

V. EXECUTIVE SUMMARY

A. Description of Ado-trastuzumab emtansine (KADCYLA) Drug Substance and Drug Product

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate comprised of the humanized IgG1 monoclonal antibody trastuzumab covalently linked to the toxin DM1 via a thioether bond. Trastuzumab is a licensed (license 1048; STN 103792) therapeutic antibody directed to an extracellular domain of HER2, a member of the EGFR family of receptors that is amplified and overexpressed in approximately 15-20% of breast cancers and is associated with aggressive tumor growth and poor clinical outcomes. DM1 is a small molecule maytansine derivative that acts as a microtubule inhibitor. The DM1 is linked to lysine residues on the trastuzumab antibody using the heterobifunctional reagent, succinimidyl trans-4-[maleimidylmethyl] cyclohexane-1-carboxylate (SMCC). The DM1 drug and resulting MCC linker make up the emtansine component of ado-trastuzumab emtansine.

<u>Drug Product:</u>
Ado-trastuzumab emtansine drug product is supplied as a lyophilized product in two single-use presentations (160 mg/vial and 100 mg/vial). Both presentations are provided as sterile, white to off-white lyophilized cakes to be reconstituted with Sterile Water for Injection (8 ml/160mg vial and 5 ml/100mg vial) to yield a preservative-free solution of 20 mg/mL ado-trastuzumab emtansine,10 mM sodium succinate, 6% w/v sucrose, and 0.02% w/v polysorbate 20, pH 5.0.

Ado-trastuzumab emtansine lyophilized drug product is to be stored at 2°C-8°C.

The 100 mg Drug Product container closure system consists of a 15 mL [redacted] (b) (4)

USP/Ph. Eur./JP Type I glass vial, sealed with a 20 mm [redacted] (b) (4) rubber lyophilization stopper, and crimped with a 20 mm aluminum seal fitted with a white plastic flip-off cap.

The 160 mg Drug Product container closure system consists of a 20 mL [redacted] (b) (4) USP/Ph. Eur./JP Type I glass vial, sealed with a 20 mm [redacted] (b) (4) rubber lyophilization stopper and a 20 mm aluminum seal fitted with purple plastic flip-off cap.

The same rubber lyophilization stopper is used for both presentations and is sealed with an aluminum seal with a plastic flip-off cap. The seal and cap do not come into contact with the Drug Product.

Ado-trastuzumab emtansine drug product does not contain any overages.

<u>Drug substance:</u>
Ado-trastuzumab emtansine drug substance is formulated at 20 mg/mL ado-trastuzumab emtansine in 10 mM sodium succinate, 6% (w/v) sucrose, and 0.02% (w/v) polysorbate 20, pH 5.0.

Ado-trastuzumab emtansine drug substance is stored [redacted] (b) (4).

<u>Environmental Assessment:</u>
A Claim of Categorical Exclusion was made under 21 CFR 25.15 (d) and 21 CFR 25.31 (b). It is stated that the use of the active moiety will be increased, but that the estimated concentration of the substance at the point of entry into the aquatic environment, based on the Estimated Introduction Concentration, will be below 1 part per billion. The sponsor furthermore states that to their knowledge no extraordinary circumstances exist.

B. Clinical Trial Information

Ado-trastuzumab emtansine (KADCYLA) is intended as a single agent for the treatment of patients with HER2 positive, [redacted] (b) (4) metastatic breast cancer who have received prior treatment with trastuzuamab and a taxane.

The route of administration of ado-trastuzumab emtansine is intravenous infusion. The recommended dosing is 3.6 mg/kg every 3 weeks (21 day cycle) until disease progression or unacceptable toxicity.

The pivotal trial (TDM4370g/BO21977, EMILIA) was a randomized, multicenter, Phase III open-label study of the efficacy and safety of ado-trastuzumab emtansine vs. lapatinib plus capecitabine in 991 randomized patients. Patients were selected based on centrally-confirmed HER2-postitivity of their tumor (IHC 3+ and/or gene amplification $\geq$ 2.0 by FISH analysis). Progression free survival (PFS), overall survival (OS), and safety were co-primary endpoints. The sponsor reported a 50% increase in PFS (9.6 months in T-DM1 vs 6.4 months in lapatinib plus capecitabine). A strong trend in OS was reported based on the interim analysis in favor of T-DM1; the final OS analysis was expected no later than first quarter, 2014. Additional supportive efficacy data were included from three Phase II studies (TDM4374g, TDM4258g, TDM4450g/BO21976).

This BLA was granted priority review status. It was submitted as a rolling BLA, with the CMC section submitted on July 31, 2012. The official submission date of the complete BLA was August 27, 2012.

C. Stability

Stability studies for drug substance and drug product were conducted in accordance with ICH Q1A(R2).

Based on the drug substance stability data provided, the following assays are stability indicating: [redacted] (b) (4) potency by bioassay, and HER2 ELISA binding assay.

<u>Drug substance:</u>

Ado-trastuzumab emtansine drug substance is stored [redacted] (b) (4) Samples for stability testing are stored [redacted] (b) (4)

Data were provided from one phase III lot following [redacted] (b) (4) long term storage (b) (4) [redacted]

Insufficient data were provided to support the proposed [redacted] (b) (4) ***shelf life. As per ICH Q1E, expiry dating is limited in the approval*** [redacted] (b) (4)***, until additional real-time supportive data are submitted to the BLA. Data from a cumulative expiry study are provided to support a shelf life of ado-trastuzumab emtansine drug substance*** [redacted] (b) (4)

Additionally, results from a cumulative expiry study supported [redacted] (b) (4) freeze/thaw cycles.

A post-approval stability protocol for drug substance was submitted (b) (4) [redacted]

Drug Product:

Ado-trastuzumab emtansine drug product is lyophilized and vialed in two single-use presentations (160 mg/vial and 100 mg/vial). The lyophilized product is to be reconstituted with Sterile Water for Injection to yield a preservative-free solution of 20 mg/mL ado-trastuzumab emtansine,10 mM sodium succinate, 6% w/v sucrose, and 0.02% w/v polysorbate 20, pH 5.0.

The recommended storage temperature of ado-trastuzumab emtansine lyophilized drug product is 2-8°C.

160mg presentation: Data from 2 phase II batches and 3 registration batches were provided following storage under real-time storage conditions of 2-8°C and support an expiration dating period of 36 months for 160 mg/vial ado-trastuzumab emtansine drug product when stored at 2-8°C.

100mg presentation: Data were provided for 3 registration batches following storage at 2-8°C for up to 18 months. Under accelerated conditions of 25°C for 6 months, no significant degradation was detected. Therefore as per ICH Q1E, the data support a shelf life of 24 months for 100 mg/vial ado-trastuzumab emtansine drug product when stored at 2-8°C.

A temperature cycling study was presented and supported the proposed maximum allowable time under ambient conditions of 744 hours (including 672 hours at ambient condition (9°C- 30°C), 48 hours at 40°C, and 24 hours at 50°C).

A photostability study was performed on 100mg registration batch and indicated no significant changes reflecting product degradation.

A post-approval stability protocol for drug product was submitted and includes the following tests, each to be performed following 0, 12, 24 and 36 months under real-time storage conditions of 2-8°C: Clarity/opalescence, color, appearance; pH, [redacted] (b) (4) protein content, DAR, purity by SE-HPLC (protein size heterogeneity), purity by RP-HPLC [redacted] (b) (4), potency by bioassay, reconstitution time, visible particles, sub-visible particles, container closure integrity. ***During the review cycle, the sponsor amended the drug product post approval stability protocol to add the***

ELISA binding assay and reconstitution time, and [redacted] (b) (4) ***the specifications for*** [redacted] (b) (4) ***purity by RP-HPLC, potency by bioassay and ELISA binding.***

The expiration dating period for ado-trastuzumab emtansine drug substance and drug product [redacted] (b) (4) by reporting data to the BLA Annual Report.

Data were provided on the stability of ado-trastuzumab emtansine post-reconstitution at room temperature for 24 hours. However, because no data were provided regarding growth promotion under these conditions, the package insert was amended to state: [redacted] (b) (4)

Ado-trastuzumab emtansine is administered intravenously. The reconstituted lyophilisate is to be diluted in an IV bag containing saline (0.9%) to a concentration [redacted] (b) (4) for infusion through a 0.2µm pore size rating in-line filter. (The pivotal trial was done using 0.45% saline, which would not require an in-line filter [redacted] (b) (4). Data provided support the stability of ado-trastuzumab emtansine diluted for intravenous administration for 25 hours following storage at 5°C or 30°C. However, because no data were provided regarding growth promotion under these conditions, the label states that the diluted KADCYLA infusion solution should be used immediately or stored at 2°C to 8°C (36°F to 46°F) for up to 4 hours prior to use.

D. Complexity/Critical Quality Attributes

Critical quality attributes related to product variants of ado-trastuzumab emtansine have been identified as drug distribution, [redacted] (b) (4) and [redacted] (b) (4)

Ado-trastuzumab emtansine is a mixture of drug-loaded species with an average drug:antibody ratio (DAR) of 3.5 (acceptable range [redacted] (b) (4)) and a range of 0-8 molecules of DM1 per antibody molecule. [redacted] (b) (4)

Proposed specifications did not include direct measure of free antibody. The sponsor has used iCIEF and MS as characterization methods to measure unconjugated antibody throughout product development and has committed to validating iCIEF as a drug substance lot release method as a PMR initiated by ONDQA. In the interim, the iCIEF and MS characterization methods will be used to control for unconjugated antibody content. RP-HPLC is used to detect free DM1 level [redacted] (b) (4)

Ado-trastuzumab emtansine is [redacted] (b) (4)

Based on process development studies, it was detemined [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

The cell based potency assay was demonstrated to be more sensitive to changes in DAR than the ELISA binding assay. However, stability studies under stressed conditions indicated that the ELISA binding assay is more sensitive to detecting degradation due to elevated temperature. Similarly, the ELISA assay, but not the cell based potency assay, was sensitive to oxidation levels. Therefore, during the review cycle the sponsor agreed to retain the ELISA binding assay as a second potency assay for lot release and the post-approval stability protocol.

(b) (4) [redacted]

This BLA is not claimed as a Quality by Design submission. However, elements of Quality by Design were incorporated into the manufacturing processes of ado-trastuzumab emtansine bulk drug substance and drug product. Multivariate Acceptable Range (MAR) and Proven Acceptable Range (PAR) were determined for most steps in the manufacturing process; Risk Ranking and Filtering (RFF) was utilized in the control of drug substance impurities; and Design of Experiment (DoE) was used in the process development for drug substance and pharmaceutical development for drug product.

E. Mechanism of Action

The primary mechanism of action of ado-trastuzumab emtansine is through targeted delivery and release of the DM1 toxin within HER2-overexpressing cancer cells. The trastuzumab component of ado-trastuzumab emtansine binds domain IV of the extracellular domain of HER2 with a K_D similar to that of trastuzumab alone. Upon binding, ado-trastuzumab emtansine undergoes receptor mediated internalization, lysosomal degradation and release of the toxin (primarily lysine-MCC-DM1). Once inside the cell, DM1 binds to tubulin and inhibits tubulin polymerization, leading to G2/M arrest and apoptotic cell death. The MCC linker was designed to increase targeted cell delivery with limited systemic release.

Ado-trastuzumab emtansine also retains established mechanisms of action of trastuzumab. It displays similar binding affinity to HER2 ECD as trastuzumab, and binds Fcγ receptors, FcRn, and C1q. It has been shown to mediate ADCC, and is also reported to inhibit shedding of the HER2 ECD and to block signaling through the P13K pathway.

There are two potency assays that are used for ado-trastuzumab emtansine: an ELISA binding assay and a cell based potency assay. The ELISA binding assay utilizes anti-DM1-coated microtiter plates for capture, and biotinylated HER2 ECD with streptavidin-HRP and substrate for visualization. The cell based potency assay is an AlamarBlue based assay that measures viability of BT-474 cells.

F. Manufacturing Process

Traztuzumab bulk drug substance as per STN 103792 is used as the trastuzumab intermediate. Trastuzumab is a humanized IgG1κ monoclonal antibody expressed in Chinese hamster ovary (CHO) cells. It is comprised of [redacted] (b) (4)

[redacted] (b) (4)

There are currently 3 approved sites under the Herceptin license for manufacture of trastuzumab bulk drug substance: Genentech Vacaville, Roche Singapore, and Roche Penzberg. The Vacaville and Singapore sites both use [redacted] (b) (4) of trastuzumab drug substance, whereas the Penzberg site utilizes [redacted] (b) (4) (identified on inspection of Penzberg facility by Linan Ha, [redacted] (b) (4), during review of STN 103792/5275). Neither shipping validation nor freeze/thaw validation [redacted] (b) (4) utilized at the Penzberg manufacturing site were provided in this submission. During the review cycle, Genentech agreed to withdraw Roche Penzberg as a supplier of trastuzumab intermediate. ***Validated studies to support shipping and freeze/thaw processes of trastuzumab bulk drug substance*** [redacted] (b) (4) ***used at Roche Penzberg will be required for the implementation of Roche Penzberg as a manufacturing site for trastuzumab intermediate for the manufacture of ado-trastuzumab emtansine.***

The manufacturing process of T-DM1 occurs [redacted] (b) (4)

Pilot scale or scale down models were used for process characterization and verification studies [redacted] (b) (4) Process validation studies [redacted] (b) (4) were performed on full scale lots.

Numerous changes to the manufacuturing process were implemented throughout the development program for ado-trastuzumab emtansine. [redacted] (b) (4)

[redacted] (b) (4)

The following parameters were identified as critical process parameters in the manufacture of ado-trastuzumab emtansine: [redacted] (b) (4)

G. Comparability

At each point outlined above when manufacturing changes were introduced, the comparability protocols and results were reviewed. Based on analytical characterization, the materials pre- and post-change were deemed comparable.

The pivotal Phase III study used drug substance manufactured at the commercial scale and the lyophilized drug product configurations (160mg/vial and 100mg/vial).

H. Immunogenicity

Two assays to detect anti-therapeutic antibodies (ATA) in patient serum were developed and used in clinical trials of ado-trastuzumab emtansine.

The first assay was an electrochemiluminescence assay (ECLA) based on the Bioveris® platform. Samples were incubated with ado-trastuzumab emtansine labeled with either biotin or ruthenium. Streptavidin coated paramagnetic beads were added and samples were read on a BioVeris M384 analyzer. The assay was validated (validation report: 4.HERc.7_AVR_1) and used for analysis of samples from Study TDM3569g (phase I, safety) and Study TDM4258g (phase II, efficacy and safety).

After the Bioveris® technology was discontinued from the market, a bridging Enzyme-linked immunosorbent assay (ELISA) was developed. Samples were incubated with a mix of biotin labeled ado-trastuzumab emtansine and digoxigenin conjugated ado-trastuzumab emtansine and transferred to a streptavidin coated plate. Horseradish peroxidase (HRP)-conjugated mouse anti-digoxigenen antibody, followed by tetramethyl benzidine peroxidase substrate were added for detection. This assay was validated (validation report: BA.MET.HERc.008.AVR_1) for the following analytical attributes: minimum dilution, minimum reportable titer, cutpoint multiplication factor, relative sensitivity, immunodepletion threshold, recovery, intra-assay precision, inter-assay precision, cross-reactivity, interference and reagent and analyte stability. The assay was then transferred to [redacted] (b) (4); an assay transfer validation report was provided. This assay was used to support the phase III study, TDM4370g/BO21977, as well as Phase II studies: TDM4374g, TDM4450g/BO21976, TDM4688g. A three-tiered approach is used in ATA detection: 1) an ELISA screen to detect ATA; 2) immunodepletion with trastuzumab emtansine and/or trastuzumab to confirm specificity; and 3) dilution of a confirmed positive sample to determine a titer value. The relative sensitivity of the assay was determined to be 52 ng/mL. The assay was capable of detecting 500ng/mL ATA in the presence of ado-trastuzumab emtansine serum levels of 10ug/mL (expected level at the time of sampling is approximately 1ug/mL). Product interference was observed with 125 ng/mL anti-T-DM1 antibodies in the presence of 10µg/mL serum T-DM1. Immunodepletion was considered positive if $\geq$ 50% and >31% of the signal was decreased following incubation with T-DM1 and trastuzumab, respectively. Neutralizing activity of ATA has not been assessed. The ELISA method is deemed sufficiently sensitive and the validation appears adequate for the detection of anti-ado-trastuzumab antibodies in the current patient population. However, as stated in the FDA guidance "Assay Development for Immunogenicity Testing of Therapeutic Proteins", the sponsor should address the functional or physiological consequences of product immunogenicity. This will be addressed as a post-marketing commitment.

The review of these two assays provided in module 5.3.1.4 can be found in the primary review memo from DMA.

VI. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Kathleen A. Clouse, Ph.D., Director Division of Monoclonal Antibodies	
Wendy C. Weinberg, Ph.D., Team Leader, Division of Monoclonal Antibodies	

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

/s/

WENDY C WEINBERG
01/30/2013

KATHLEEN A CLOUSE STREBEL
01/30/2013

Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date:	October 24, 2012
From:	Bo Chi, Ph.D., OC/OMPQ/DGMPA/BMAB Linan Ha, Ph.D., OPS/OBP/DMA
To:	BLA File, STN 125427/0
Through:	Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject:	New Biologic License Applications (BLA)
Applicant:	Genentech, Inc.
Facility:	Roche Diagnostics GmbH, Nonnenwald 2, D-82377 Penzberg, Germany FEI: 3002806560
Product:	trastuzumab emtansine
Dosage:	100 mg and 160 mg vials (20 mg/ml), Sterile lyophilized single use vial, intravenous infusion
Indication:	Single agent for treatment of patients with HER2-positive metastatic breast cancer

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that Roche Penzberg is currently approved to manufacture trastuzumab, we recommend that the pre-approval inspection of the Roche Penzberg facility (FEI# 3002806560) be waived for STN125427/0.

Clearance Routing

David Doleski **CONCUR/ NONCONCUR DATE** 11/20/2012

David Doleski,
Director, Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality, Office of Compliance, CDER

Kathleen A. Clouse **CONCUR/ NONCONCUR DATE** 11/07/2012

Kathleen A. Clouse, Ph.D.
Director, Division of Monoclonal Antibodies, Office of Biotechnology Products,
Office of Pharmaceutical Science, CDER

Summary

BLA STN125427/0 was submitted by Genentech for trastuzumab emtansine, an antibody-drug conjugate (ADC) for treatment of patients with HER2-positive metastatic breast cancer and who have relapsed from prior HER2-directed treatments. Trastuzumab emtansine consists of the antibody trastuzumab (humanized anti-HER2 IgG1) conjugated via a thioether bond to the cytotoxic microtubule-inhibitory maytansinoid, DM1. The approved drug substance manufacturing sites for the monoclonal antibody trastuzumab include Genentech, Vacaville, CA; Roche Diagnostics GmbH, Penzberg, Germany; and Roche Singapore Technical, Singapore.

<u>Facility information</u>

This BLA proposes to use the approved drug substance manufacturing sites for trastuzumab to manufacture trastuzumab, one of the two intermediates for trastuzumab emtansine. The manufacturing process of trastuzumab includes [redacted] (b) (4)

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

   The Roche Penzberg facility is currently approved to manufacture trastuzumab. No change has been made to the approved manufacturing process for trastuzumab in the trastuzumab emtansine BLA.

2. *FDA has not inspected the establishment in the last 2 years.*

   Inspected by 1/9/12-1/17/12 by CDER-OMPQ and CDER-OBP and classified VAI. This was a preapproval/pre-license inspection to cover the trastuzumab manufacturing operations under STN 103792/5275.

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

   The preapproval/pre-license inspection on1/9/12-1/17/12 found this site acceptable and the supplement was approved. It was the first FDA inspection of [redacted] (b) (4) area [redacted] (b) (4) of the Roche Penzberg facility.

4. *The establishment is performing* [redacted] (b) (4)

   The Roche Penzberg facility is currently approved to manufacture trastuzumab. There is no change to the approved manufacturing process proposed in the new BLA.

5. *The manufacturing process is* [redacted] (b) (4) [redacted] *produced by the establishment.*

The Roche Penzberg facility is currently approved to manufacture trastuzumab. There is no change to the approved manufacturing process proposed in the new BLA.

Signed:

Bo Chi, Ph.D. ____________ Date 11/5/12
Microbiologist
OC/OMPQ/DGMPA/BMAB

Linan Ha, Ph.D. ____________ Date 11/7/12
Senior staff Fellow
OPS/OBP/DMA

Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date:	October 24, 2012
From:	Bo Chi, Ph.D., OC/OMPQ/DGMPA/BMAB Linan Ha, Ph.D., OPS/OBP/DMA
To:	BLA File, STN 125427/0
Through:	Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject:	New Biologic License Applications (BLA)
Applicant:	Genentech, Inc.
Facility:	Genentech, 1000 New Horizons Way, Vacaville, CA 94080 FEI: 3002902534
Product:	trastuzumab emtansine
Dosage:	100 mg and 160 mg vials (20 mg/ml), Sterile lyophilized single use vial, intravenous infusion
Indication:	Single agent for treatment of patients with HER2-positive metastatic breast cancer

Waiver Recommendation
We recommend that the pre-approval inspection of the Genentech Vacaville facility (FEI# 3002902534) be waived for STN125427/0. A surveillance inspection of the facility has been scheduled and will be conducted by ORA/SAN-DO in early December, 2012.

Clearance Routing

David Doleski CONCUR/NONCONCUR DATE 11/20/2012
David Doleski,
Director, Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality, Office of Compliance, CDER

Kathleen A. Clouse CONCUR/ NONCONCUR DATE 11/07/2012
Kathleen A. Clouse, Ph.D.
Director, Division of Monoclonal Antibodies, Office of Biotechnology Products,
Office of Pharmaceutical Science, CDER

Summary

BLA STN125427/0 was submitted by Genentech for trastuzumab emtansine, an antibody-drug conjugate (ADC) for treatment of patients with HER2-positive metastatic breast cancer and who have relapsed from prior HER2-directed treatments. Trastuzumab emtansine consists of the antibody trastuzumab (humanized anti-HER2 IgG1) conjugated via a thioether bond to the cytotoxic microtubule-inhibitory maytansinoid, DM1. The approved drug substance manufacturing sites for the monoclonal antibody trastuzumab include Genentech, Vacaville, CA; Roche Diagnostics GmbH, Penzberg, Germany; and Roche Singapore Technical, Singapore.

<u>Facility information</u>

This BLA proposes to use the approved drug substance manufacturing sites for trastuzumab to manufacture trastuzumab, one of the two intermediates for trastuzumab emtansine. The manufacturing process of trastuzumab includes [redacted] (b) (4)

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

   The Genentech Vacaville facility is currently approved to manufacture trastuzumab. No change has been made to the approved manufacturing process for trastuzumab in the trastuzumab emtansine BLA. Other approved products manufactured at the facility include bevacizumab, omalizumab, and rituximab.

2. *FDA has not inspected the establishment in the last 2 years.*

   Inspected by SAN-DO from 6/15/10-6/23/10 and classified NAI. A surveillance inspection of the facility has been scheduled and will be conducted by ORA/SAN-DO in early December, 2012.

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

   The previous CGMP inspection from 6/15/10-6/23/10 found the CBI profile updated and acceptable. This site was also found acceptable for manufacturing operations for Trastuzumab under BLA 103792. No Form FDA 483 was issued.

4. *The establishment is performing* [redacted] (b) (4)

   The Genentech Vacaville facility is currently approved to manufacture trastuzumab. There is no change to the approved manufacturing process proposed in the new BLA.

5. *The manufacturing process is* [redacted] (b) (4) *produced by the establishment.*

The Genentech Vacaville facility is currently approved to manufacture trastuzumab. There is no change to the approved manufacturing process proposed in the new BLA.

Signed:

Bo Chi, Ph.D. Bo Chi Date 11/5/12
Microbiologist
OC/OMPQ/DGMPA/BMAB

Linan Ha, Ph.D. Linan Ha Date 11/7/12
Senior staff Fellow
OPS/OBP/DMA

Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date:	October 24, 2012
From:	Bo Chi, Ph.D., OC/OMPQ/DGMPA/BMAB Linan Ha, Ph.D., OPS/OBP/DMA
To:	BLA File, STN 125427/0
Through:	Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject:	New Biologic License Applications (BLA)
Applicant:	Genentech, Inc.
Facility:	Roche Singapore Technical, 10 Tuas Baylink, Singapore FEI: 3007164129
Product:	trastuzumab emtansine
Dosage:	100 mg and 160 mg vials (20 mg/ml), Sterile lyophilized single use vial, intravenous infusion
Indication:	Single agent for treatment of patients with HER2-positive metastatic breast cancer

Waiver Recommendation
Based on the compliance history of the firm, the current GMP status, and the fact that Roche Singapore is currently approved to manufacture trastuzumab, we recommend that the pre-approval inspection of the Roche Singapore facility (FEI# 3007164129) be waived for STN125427/0.

Clearance Routing

David Doleski (signature) CONCUR/ NONCONCUR DATE 11/20/2012
David Doleski,
Director, Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality, Office of Compliance, CDER

Kathleen A. Clouse (signature) CONCUR/ NONCONCUR DATE 11/07/2012
Kathleen A. Clouse, Ph.D.
Director, Division of Monoclonal Antibodies, Office of Biotechnology Products,
Office of Pharmaceutical Science, CDER

Summary

BLA STN125427/0 was submitted by Genentech for trastuzumab emtansine, an antibody-drug conjugate (ADC) for treatment of patients with HER2-positive metastatic breast cancer and who have relapsed from prior HER2-directed treatments. Trastuzumab emtansine consists of the antibody trastuzumab (humanized anti-HER2 IgG1) conjugated via a thioether bond to the cytotoxic microtubule-inhibitory maytansinoid, DM1. The approved drug substance manufacturing sites for the monoclonal antibody trastuzumab include Genentech, Vacaville, CA; Roche Diagnostics GmbH, Penzberg, Germany; and Roche Singapore Technical, Singapore.

<u>Facility information</u>

This BLA proposes to use the approved drug substance manufacturing sites for trastuzumab to manufacture trastuzumab, one of the two intermediates for trastuzumab emtansine. The manufacturing process of trastuzumab includes [redacted] (b) (4)

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

   The Roche Singapore facility is currently approved to manufacture trastuzumab. No change has been made to the approved manufacturing process for trastuzumab in the trastuzumab emtansine BLA.

2. *FDA has not inspected the establishment in the last 2 years.*

   Inspected by IOG from 4/26/12-5/3/12 and classified VAI. This was a CGMP inspection.

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

   The previous inspection found this site acceptable for manufacturing operations for Trastuzumab under BLA 103792.

4. *The establishment is performing* [redacted] (b) (4)

   The Roche Singapore facility is currently approved to manufacture trastuzumab. There is no change to the approved manufacturing process proposed in the new BLA.

5. *The manufacturing process is* [redacted] (b) (4) *produced by the establishment.*

The Roche Singapore facility is currently approved to manufacture trastuzumab. There is no change to the approved manufacturing process proposed in the new BLA.

Signed:

Bo Chi, Ph.D. _Bo Chi_ Date 11/5/12
Microbiologist
OC/OMPQ/DGMPA/BMAB

Linan Ha, Ph.D. _Linan Ha_ Date 11/7/12
Senior staff Fellow
OPS/OBP/DMA

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

/s/

BO CHI
11/21/2012

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	**Applicant:**	**Stamp Date:**
STN-125427	**Genentech, Inc.**	**August 24, 2012**
Established/Proper Name: Trastuzumab emtansine	**BLA/NDA Type:** BLA	

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y N Y N	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Labeling:	Y N	
❑ PI –non-annotated	Y N	
❑ PI –annotated	Y N	An annotated table is provided.
❑ PI (electronic)	Y N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y N	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	Per 356h (USAN: trastuzumab
❑ proprietary name (for review)	Y N	emtansine)

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Quality overall summary [2.3] ❑ Drug Substance ❑ Drug Product ❑ Facilities and Equipment ❑ Adventitious Agents Safety Evaluation ❑ Novel Excipients ❑ Executed Batch Records ❑ Method Validation Package ❑ Comparability Protocols	Y N Y N Y N Y N Y N Y N Y N Y N Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S] ❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ description of manufacturing process and process control o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping ❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing ❑ control of critical steps and intermediates o justification of specifications o stability	 Y N Y N Y N Y N Y N	Cell substrate and cell banking system: not applicable, the submission cross references trastuzumab BLA (STN: BL103792) for the production of the antibody intermediate. The submission states that only FDA licensed trastuzumab Drug Substance will be used in the manufacturing of trastuzumab emtansine.

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y N	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
❑ characterization of drug substance		
❑ control of drug substance		
o specifications	Y N	
o justification of specs.	Y N	
o analytical procedures		
o analytical method validation		
o batch analyses	Y N	
❑ reference standards	Y N	
❑ container closure system		
❑ stability	Y N	
❑ summary	Y N	
❑ post-approval protocol and commitment	Y N	
❑ pre-approval		
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y N	
❑ pharmaceutical development	Y N	
o preservative effectiveness	Y N	
o container-closure integrity	Y N	
	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation		
o Component, container,		

CTD Module 3 Contents	Present?	If not, justification, action & status
closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y N	
❑ reference standards or materials	Y N	
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y N	
Diluent (vials or filled syringes) [3.2P′]		
❑ description and composition of diluent	Y N	Not applicable. Diluent to be used is SWFI. No additional information is provided.
❑ pharmaceutical development	Y N	
o preservative effectiveness	Y N	
o container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing		

CTD Module 3 Contents	Present?	If not, justification, action & status
process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N Y N	
❑ controls of critical steps and intermediates		
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program	Y N	
o Lyophilizer sterilization validation o Other needed validation data (hold times)	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF & LOAs	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results		
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices	Y N	Not applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ other marketed chemicals (e.g. part of kit)	Y N	
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y N Y N Y N	*Note:* Cell line qualification, viral testing of unprocessed bulk and viral clearance studies: Not applicable. The submission cross references trastuzumab BLA (STN: BL103792) for the production of the antibody intermediate.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y N Y N	
Literature references and copies [3.3]	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y N	
Includes data demonstrating consistency of manufacture	Y N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	
Describes changes in the manufacturing	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
process, from material used in clinical trial to commercial production lots		
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
Certification that all facilities are ready for inspection	Y N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: □ LAL instead of rabbit pyrogen □ mycoplasma □ sterility	Y N Y N Y N Y N	Mycoplasma: Not applicable. The submission cross references trastuzumab BLA (STN: BL103792) for the production of the antibody intermediate.
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes No

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

	9/18/2012
Product Quality Reviewer(s)	Date
	9/18/2012
Branch Chief/Team Leader/Supervisor	Date
Kathleen A. Clouse	09/18/2012
Division Director	Date

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

/s/

LISA M SKARUPA
10/19/2012

LINAN HA
10/22/2012

WENDY C WEINBERG
10/22/2012

KATHLEEN A CLOUSE STREBEL
10/22/2012

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	**Applicant:**	**Stamp Date:**
STN125427	**Genentech**	**September 14, 2012**
Established/Proper Name: USAN: trastuzumab emtansine	**BLA/NDA Type:** **Priority**	

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y N	Not required.
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	Defer to OBP and OND.

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
guidance)		
Companion application received if a shared or divided manufacturing arrangement	Y N	N/A

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	Not required.
Introduction to the summary documents (1 page) [2.2]	N	Not required.
Quality overall summary [2.3] ❑ Drug Substance ❑ Drug Product ❑ Facilities and Equipment ❑ Adventitious Agents Safety Evaluation ❑ Novel Excipients ❑ Executed Batch Records ❑ Method Validation Package ❑ Comparability Protocols	Y Y Y Y Y Y Y Y N	 N/A

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	Not required.
Drug Substance [3.2.S] ❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ description of manufacturing process and process control o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping ❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history,	 Y Y Y Y	The BLA refers to the trastuzumab BLA STN103792 for the information on the trastuzumab antibody intermediate. (description of manufacturing process) The BLA refers to the trastuzumab BLA STN103792 for the information on the trastuzumab antibody intermediate. (control of materials)

CTD Module 3 Contents	Present?	If not, justification, action & status
and generation o cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	Y	
o justification of specifications o stability		
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance	Y	
❑ control of drug substance	Y	
o specifications o justification of specs. o analytical procedures o analytical method validation o batch analyses		
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol o results o method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness		
o container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging	Y	

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
(including all steps performed at outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y	
o Filter validation	Y	Validation of sterilizing [redacted] (b) (4) is missing. It will be requested.
o Component, container, closure depyrogenation and sterilization validation	Y	Validation [redacted] (b) (4) is missing. It will be requested
o Validation of aseptic processing (media simulations)	Y	
o Environmental Monitoring Program	Y	
o Lyophilizer validation	Y	
o Other needed validation data (hold times)	Y	Thaw DS hold time validation is missing for microbial quality. It will be requested.
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	N	N.A.
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y	
❑ container closure system [3.2.P.7]	Y	
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs		
o administration device(s)		
❑ stability	Y	
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol		
o results		
o method validation		
Diluent (vials or filled syringes) [3.2P′]		N/A
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
○ preservative effectiveness	Y N	
○ container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation	Y N	
○ Validation of aseptic processing (media simulations)		
○ Environmental Monitoring Program	Y N Y N	
○ Lyophilizer sterilization validation		
○ Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
○ specifications (vial, elastomer, drawings)		
○ availability of DMF & LOAs		

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y N Y N	N/A
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y Y N Y N	 Defer to OBP. Defer to OBP.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y Y N	 Defer to OBP. N/A
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Defer to OBP.
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to OBP.
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to OBP.
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	Defer to OBP.
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y N Y Y N Y	 Defer to OBP.
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	Defer to OBP.
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Bo Chi, PhD	September 14, 2012
Product Quality Reviewer	Date

Reyes Candau-Chacon, PhD	September 14, 2012
Product Quality Reviewer	Date

Patricia Hughes, PhD	September 14, 2012
Team Leader	Date

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

/s/

REYES CANDAU-CHACON
09/14/2012

BO CHI
09/14/2012

PATRICIA F HUGHES TROOST
09/14/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

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

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

Note: All manufacturing[3] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: Unknown. This is a rolling BLA. The last module has not been submitted yet. However, OND would like all the inspection related activities completed by the end of November 2012.

Applicant Name: Genentech, Inc.

U.S. License #: 1048

STN(s): STN125427/0

Product(s): trastuzumab-MCC-DM1 (trastuzumab emtansine, T-DM1)

Short summary of application: New BLA

FACILITY INFORMATION

Manufacturing Location: Antibody intermediate manufacturing site

Firm Name: Genentech

Address: 1000 New Horizons Way
Vacaville, CA 94080

FEI: 3002902534

Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for Trastuzumab intermediate

Inspected by SAN-DO from 6/15/10-6/23/10 and classified NAI. This CGMP inspection found the CBI profile updated and acceptable. This site was also found acceptable for manufacturing operations for Trastuzumab under BLA 103792. A routine surveillance for this site is also an FY 13 performance goal and is being planned by SAN-DO. This site is considered acceptable for the purposes of this BLA at this time, however, an evaluation of the pending surveillance inspection will also be used to determine CGMP compliance of this facility.

Manufacturing Location: Antibody intermediate manufacturing site

Firm Name: Roche Singapore Technical Operations PTe. Ltd.

Address: Singapore 637394

FEI: 3007164129

Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for Trastuzumab intermediate

Inspected by IOG from 4/26/12-5/3/12 and initially classified VAI. This was a CGMP inspection. This site was also found acceptable for manufacturing operations for Trastuzumab under BLA 103792. Action on this BLA should not be taken until this inspection classification is finalized.

Manufacturing Location: Antibody intermediate manufacturing site
Firm Name: Roche Diagnostics GmbH
Address: Pharma Biotech Penzberg
Nonnenwald 2
D-82377
Penzberg, Germany
FEI: 3002806560
Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for Trastuzumab intermediate

Inspected by 1/9/12-1/17/12 by CDER-OMPQ and classified VAI. This was a pre approval inspection to cover Trastuzumab operations under STN 103792/5275. This site was found acceptable and the supplement was approved. This site is considered acceptable for the purposes of this BLA.

Manufacturing Location: DM1 intermediate manufacturing site
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for DM1 intermediate

Inspected (b) (4) and classified NAI. This CGMP inspection found the (b) (4) profiles updated and acceptable. The manufacture of the DM1 intermediate is considered (b) (4), therefore the current compliance history is adequate to provide an acceptable recommendation for this facility in support of this BLA.

Manufacturing Location: DM1 intermediate manufacturing site
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for DM1 intermediate

Inspected (b) (4) and classified VAI. This CGMP inspection found the (b) (4) profile updated and acceptable. The manufacture of the DM1 intermediate is considered (b) (4), therefore the current compliance history is adequate to provide an acceptable recommendation for this facility in support of this BLA

Manufacturing Location: Testing site
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: (b) (4) Testing

Inspected [redacted] (b) (4) and classified NAI. This inspection covered control testing operations which included [redacted] (b) (4) testing. The CTL profile was updated and found acceptable.

Manufacturing Location: Drug substance manufacturing site
Firm Name: [redacted] (b) (4)
Address: [redacted] (b) (4)

FEI: [redacted] (b) (4)
Short summary of manufacturing activities performed: Manufacture, Lot Release Testing, and Stability Testing for drug substance and drug product

Inspected by CDER-DMPQ [redacted] (b) (4) and classified VAI. This comprehensive pre-approval inspection found drug substance manufacturing operations acceptable for another BLA, however found the BTP profile updated and acceptable. Due to the complexity of the drug substance manufacturing and linking operations, BMAB is planning to inspect this facility in support of this BLA. Action on this BLA should not be taken until this inspection is completed and reviewed for compliance to CGMP for the operations listed.

Manufacturing Location: Drug product manufacturing site
Firm Name: [redacted] (b) (4).
Address: [redacted] (b) (4)

FEI: [redacted] (b) (4)
Short summary of manufacturing activities performed: Manufacture of DP, sterility and endotoxin testing for lot release

Inspected [redacted] (b) (4) and classified VAI. This was a CGMP inspection that provided coverage for sterile operations, including manufacturing [redacted] (b) (4). The SVS profile was updated and found acceptable.

Manufacturing Location: DP packaging
Firm Name: Genentech
Address: 4625 Brookwood Parkway
Hillsboro, OR 97124
FEI: 3007232634
Short summary of manufacturing activities performed: Labeling and packaging

Inspected by CDER-OMPQ from 6/19/12-6/27/12 and classified VAI. This inspection provided coverage to packaging and labeling operations and found them acceptable.

OVERALL RECOMMENDATION:

Action on this BLA should not be taken until all relevant facility inspections have been completed and are evaluated for compliance to CGMP. Please resubmit this Tb-EER 15-30 days prior to the planned action date for an updated compliance evaluation.

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[3] The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling,

testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

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

/s/

MAHESH R RAMANADHAM
08/16/2012