

**CENTER FOR DRUG EVALUATION AND
RESEARCH AND CENTER FOR BIOLOGICS
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

125147/0

CHEMISTRY REVIEW(S)



Review Cover Sheet

BLA STN 125147/0

VECTIBIX™ (Panitumumab)

Amgen, Inc

Chana Fuchs, Ph.D. HFD-123
Ruth Cordoba-Rodriguez, Ph.D. HFD-123
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science



CMC Review Data Sheet

1. **BLA#** STN 125147/0
2. **REVIEW #:** 1
3. **REVIEW DATE:** 22-SEP-2006
4. **REVIEWERS:** Chana Fuchs, Ph.D.
Ruth Cordoba-Rodriguez, Ph.D.
5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS¹:**

<u>Previous Documents</u>	<u>Document Date²</u>
Clinical Pre-BLA Meeting	24-MAY-2005
CMC Pre-BLA Meeting	26-MAY-2005
Facilities meeting	19-May-2005
PMA meeting	15-SEP-2005
CMA pilot 1 meeting	19-OCT-2005
Pre-BLA meeting	22-NOV-2005
Pre-PMA meeting	22-NOV-2005
Post submission briefing	15-MAY-2006
Filing Review (45 days).	26-MAY-2006
— 483	02-JUN-2006
Amgen Fremont 483	05-JUN-2006
Filing Deficiency Letter	06-JUN-2006
CMC Discipline Review Letter	29-AUG-2006
T-com	08-MAY-2006
T-com	22-MAY-2006
T-com	24-MAY-2006
T-com	30-JUN-2006
T-com	06-JUL-2006
T-com	14-JUL-2006
T-com	27-JUL-2006
T-com	24-AUG-2006
T-com	25-AUG-2006
T-com	31-AUG-2006
T-com	18-SEP-2006
T-com	20-SEP-2006
E-com	25-MAY-2006
E-com	25-MAY-2006
E-com	26-MAY-2006
E-com	20-JUN-2006
E-com	06-JUL-2006
E-com	12-JUL-2006
E-com	26-JUL-2006
E-com	27-JUL-2006
E-com	27-JUL-2006
E-com	28-JUL-2006



E-com	04-AUG-2006
E-com	07-AUG-2006
E-com	10-AUG-2006
E-com	10-AUG-2006
E-com	11-AUG-2006
E-com	21-AUG-2006
E-com	23-AUG-2006
E-com	24-AUG-2006
E-com	24-AUG-2006
E-com	25-AUG-2006
E-com	08-SEP-2006
E-com	18-SEP-2006
E-com	19-SEP-2006
E-com	20-SEP-2006

¹ Chronology of previous CMC communications between CDER and the firm and/or reviews

² Applicant's letter date or date of review and/or communication with applicant

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
STN 125147/0.001 Original Submission–Quality RU	24-FEB-2006
STN 125147/0.004 CMC –re Abgenix acquisition	20-APR-2006
STN 125147/0.005 CMC-response to question (RTQ)	12-MAY-2006
STN 125147/0.007 CMC-RTQ	25-MAY-2006
STN 125147/0.008 CMC stability update	19-JUN-2006
STN 125147/0.010 CMC RTQ to ATO request	21-JUN-2006
STN 125147/0.011 CMC corrections to CMC section	23-JUN-2006
STN 125147/0.018 CMC RTQ	13-JUL-2004
STN 125147/0.019 CMC RTQ	28-JUL-2006
STN 125147/0.020 CMC RTQ	04-AUG-2006
STN 125147/0.024 CMC RTQ	04-AUG-2006
STN 125147/0.025 CMC revised specifications	25-AUG-2006
STN 125147/0.026 changes to USPI	31-AUG-2006
STN 125147/0.028 CMC response to DR letter #4 and 5	06-SEP-2006
STN 125147/0.029 CMC response to DR letter	08-SEP-2006
Response from — to the FDA 483	19-JUN-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Amgen
Address: 1 Amgen Center Drive
Thousand Oaks, CA 91320
Representative: Mary Celine Scott, Ph.D., MBA
Telephone: 805-447-3741



8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Vectibix™
- b) Non-Proprietary Name: panitumumab
- c) Code name: ABX-EGF, AMG954, ABX 10221
- d) Common name: anti-human EGFR
- e) Drug Review Status: Fast Track
- f) Chemical Type: recombinant human monoclonal antibody

9. PHARMACOL. CATEGORY: Therapeutic monoclonal antibody to Epithelial Growth Factor Receptor (EGFR)

10. DOSAGE FORM: Sterile parenteral solution.

11. STRENGTH/POTENCY:

- (i) The concentration of Vectibix (panitumumab) Drug Product is — mg/ml.
- (ii) Potency is defined as using a proprietary — bioassay. Potency specification is —
- (iii) Dating period for vialled drug product is 24 months when stored at 2°C -8°C.
- (iv) Panitumumab is filled into 5 mL, 10 mL, or 20 mL vials containing 100 mg, 200 mg, or 400 mg of panitumumab, respectively.

12. ROUTE OF ADMINISTRATION: Intravenous infusion, diluted to a total volume of 100 ml with 0.9% Sodium Chloride for Injection, USP. Doses higher than 1000mg should be diluted to 150 ml with 0.9% Sodium Chloride for Injection, USP. Final concentration should not exceed 10 mg/ml.

13. ACID (Animal Component Information Database)

Section 3.2.A.2. lists starting materials of biological origin. The animal derived raw materials used in the manufacturing process of panitumumab are represented below:

Raw Material:

Vendor:

Source

Raw Material:

Vendor:

Source:

Raw Material:

Vendor:

Source:

Lactose is used for adjustment of trypsin activity.

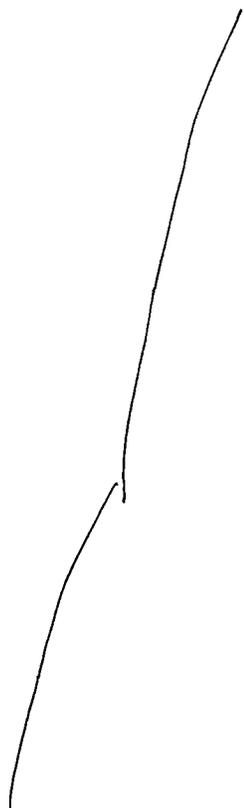
Raw Material:
Vendor:
Source:

Raw Material:
Vendor:
Source:

Raw Material:
Vendor:
Source:

Raw Material:
Vendor:
Source:

Raw Material:
Source:



**14. PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY, MAIN SPECIES
MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S:**

Panitumumab is a human IgG2 kappa isotype monoclonal antibody produced in CHO cells. It is composed of _____



The molecular weight of panitumumab is approximately 147 kDa.





15. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	V		/	3/4/7	N/A		Information for facilities and process is in the BLA. A PAI was conducted at the facility as part of the approval mechanism.
7	III			4	N/A		DP container closure system and leachables were included in the BLA.
/	III			1	Adequate	12-FEB-2003	Meets USP requirements
/	III			3	Adequate		Compliance check granted
/				4	N/A		SOPs and validation reports for assays used were submitted to the BLA

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
/	/	/

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

OBP:

CONSULTS/ CMC RELATED REVIEWS	RECOM-MENDATION	DATE	REVIEWER
Establishment Status	Approve	Compliance check completed 11-Sep-2006	Janet Barletta
Environmental Assessment	Approve	19-Sep-2006	Chana Fuchs
DMPQ – memo for Drug Substance facilities review	Approve	23-May-2006	Michelle Clark-Stewart
DMPQ – memo for Drug Product facilities review	Approve	28-Jul-2006	Janet Barletta
Carton and vial labeling	Approve	25-Aug-2006	Carole Broadnax
Carton and vial labeling	Approve		Sheila Rawls
DMA - Tradename review	Approve	7-Jun-2006	Chana Fuchs
ODS – tradename review	Approve	15-Sep-2006	
DMETS/DDMAC – tradename review	Approve	24-Feb-2006	Jinhee L. Jahng [DMETS]
EIR for Amgen –Fremont	Approve	Sep-2006	Clark-Stewart/Fuchs/Cordoba-Rodriguez
EIR for Amgen-Thousand Oaks	Approve	Sep-2006	Clark-Stewart/Fuchs/Cordoba-Rodriguez
EIR for _____	Approve	6-Sep-2006	Melendez/Barletta

Review trade name for medical error avoidance

17. **Inspectional Activities**

A pre-approval inspection (PAI) for panitumumab drug substance production at the Amgen – Fremont (AFR) facility was conducted From May 30 to June 5, 2006. AFR is responsible for manufacturing of panitumumab drug substance as well as drug substance and drug product QC testing. AFR was not previously inspected by the FDA.



A form 483 was issued at the end of this inspection. Observations consisted of failure to follow current versions of written SOPs, deficiencies in batch production/control records, deficiencies in laboratory records, and failure to document/log QC invalid results in a timely manner. This inspection is classified VAI.

A pre-approval inspection at the Amgen – Thousand Oaks (ATO) facility was conducted on June 7-8, 2006. ATO is responsible for _____ DS stability and release testing, Drug Product, release, and stability testing, and storage of Drug substance and Drug product. No Form FDA-483 was issued.

A pre-approval inspection (PAI) for panitumumab drug product manufacturing at the _____ was conducted by TFRB from May 30 to June 2, 2006. _____ is responsible for manufacturing of panitumumab drug product and for a subset of drug product release testing. A 6 observations form 483 was issued at the end of this inspection. Major inspectional issues identified that could impact the ability to license panitumumab were _____ contamination control and the problematic design of the _____ area and operations line. FDA's concern was that these do not provide adequate assurance that the firm is capable of producing sterile drug product. _____ to address these concerns, a number of follow-up meetings between _____ and FDA were conducted, where _____ initially presented their: _____ studies, and ultimately outlined their commitments on the corrections that they will be implementing. Corrective actions implemented prior to BLA approval are mainly procedural controls, while additional corrective actions to be implemented as PMCs also include facility process improvements. (see PMC section below).

Inspection at _____ was waived. This waiver was based on the criteria as required per SOPP 8410, "Determining When Pre-licensing/pre-approval Inspections(PLI/PAI) are Necessary." The review committee recommended that the inspection be waived due to the low risk of the activities performed at this site as well as to a compliance check confirming that there are no pending actions to prevent approval at this site. Activities at _____ include Drug Product storage, labeling and packaging.

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of panitumumab (Vectibix™) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets the parameters recommended by FDA. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. It is recommended that this product be approved for human use (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The sponsor has agreed to the following post-marketing commitments:

1. To oversee the implementation of design and facility controls at the _____ as stated in the response to the quality discipline review letter dated 06 September 2006. This is to begin prior to the _____ December 2006.
2. /
3. To submit proposed revisions to release specifications and shelf-life specifications for panitumumab drug substance after commercial manufacturing runs which reflect increased manufacturing experience. The proposed revisions to the quality control system, data from the commercial manufacturing runs, and the analysis plan used to support the proposed specifications will be submitted as a supplement to the BLA no later than June 2008.
4. /
5. To submit proposed revisions to release specifications and shelf-life specifications for panitumumab drug product after commercial manufacturing runs to reflect increased manufacturing experience. These revisions to the quality control system, data from the commercial manufacturing runs, and the analysis plan used to create the proposed specifications will be submitted as a supplement to the BLA no later than December 2007.
6. /
7. /

8.

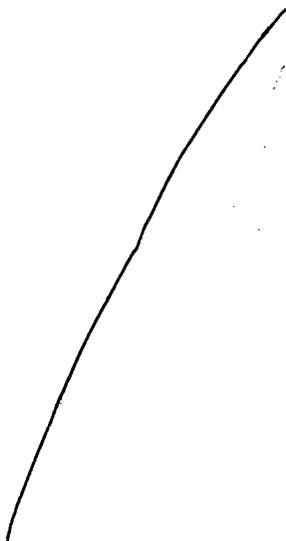
9. To include CCI testing as a component of the post approval drug product stability program using each vial configuration (5 mL, 10 mL, 20 mL) as they are added to the stability program, with testing at the _____ month time-points to demonstrate container closure integrity throughout shelf life. A supplemental stability protocol to include CCI testing will be submitted by September 2007.

II. Summary of Chemistry Assessments

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

- VECTIBIX™ (Panitumumab) is supplied as a sterile, preservative-free, colorless solution for intravenous infusion containing _____ mg/mL panitumumab monoclonal antibody in formulation buffer consisting of _____ sodium chloride, _____ sodium acetate, and water for injection, USP. It is supplied in 5 mL, 10 mL, or 20 mL single use vials containing 100 mg, 200 mg, or 400 mg of panitumumab, respectively.
- The container closure system consists of a Type I glass vial, _____ stopper, and aluminum seal with flip-off cap.
- Panitumumab may contain translucent to white proteinaceous particles that are removed by an in-line filter during infusion. The particles are derived from panitumumab and consist primarily of _____
- Stability of the panitumumab drug product has been established for up to 24 months at 2° to 8° C for all 3 vial configurations (5, 10 and 20 mL).
- Panitumumab is a recombinant, human IgG2 kappa monoclonal antibody _____

The molecular weight of panitumumab is approximately 147 kDa,



- Panitumumab is produced in genetically engineered mammalian (Chinese Hamster Ovary) cells at the _____ scale using a _____



- Although some animal-derived raw materials are used in the manufacture of Vectibix™, measures such as testing of _____ and raw materials, lot traceability, and acceptance criteria have been implemented to prevent product contamination from potential viral and non-viral adventitious agents.
- The panitumumab drug substance manufacturing process has been modified a number of times during clinical development. Biochemical comparability study results between successive processes were submitted and reviewed under IND for appropriateness. A significant change in manufacturing was implemented prior to initiation of pivotal trials with a switch from murine hybridoma to CHO cell substrate, change in manufacturing facility and in the manufacturing process. Biochemical and biophysical analysis, nonclinical and a small clinical pharmacokinetic (PK) comparability studies showed that although there were some biochemical and biophysical differences between panitumumab produced by the 2 processes, there was sufficient supporting data to say

that product from the clinical CHO process was, by *in vitro* data, functionally equivalent to product from the hybridoma. The preclinical and clinical data found them sufficiently similar for use in the pivotal clinical study and ongoing clinical trials. The pivotal trials used panitumumab produced at Amgen Washington from CHO cells at the _____ scale. The commercial product is produced at Amgen Fremont from CHO cells at the _____ scale. A comparability study was submitted to the BLA. Based on biochemical and biophysical data submitted, the clinical and commercial products appear comparable. However, differences were noted between the products from these 2 manufacturing processes in both animal and human PK. Additional clinical safety data was requested to support licensure of the commercial product. Panitumumab drug product manufacturing has also undergone manufacturing changes ranging from facility changes, concentration and vial size. Panitumumab concentration was increased from _____ mg/mL with the implementation of the CHO clinical manufacturing process. Vial size increased from 5 to 10 mL to accommodate the larger clinical dose. Other than concentration of panitumumab, the formulation and excipients have remained the same throughout development. Clinical drug product used in the pivotal trial was produced at Amgen Thousand Oaks (ATO), while commercial drug product will be manufactured at _____

- Panitumumab has _____ degradation: _____
 _____ degradation may exacerbate one or more of the
 following product-related impurities or modifications present in a typical panitumumab
 DP sample: _____

_____ Panitumumab degradation can be monitored by _____

- Panitumumab binds the L2 ligand binding domain of the Epidermal Growth Factor Receptor (EGFR) with an affinity of $K_d = 5 \times 10^{-11}$ M, thereby blocking ligands (e.g. EGF and TGF- α) from binding to the receptor. Ligand binding to the EGFR induces homo- or hetero-dimerization with other members of the ErbB receptor family, resulting in receptor autophosphorylation and downstream signaling. Ligand induced homodimers signal mainly through the MAPK pathway resulting in a proliferation signal, while ligand induced heterodimers signal through the MAPK and PI3K pathways, resulting in activation of both proliferation and survival intracellular signals. *In vitro* studies show that binding of panitumumab to EGFR inhibits ligand induced receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of extracellular acidification and cell proliferation, induction of apoptosis, decreased pro-inflammatory cytokine and vascular growth factor production, and internalization of the EGFR. Internalization of the EGFR by panitumumab is less pronounced and has slower kinetics compared to internalization induced by EGF.



- As an IgG2 isotype monoclonal antibody, panitumumab is expected to have reduced Fc domain based effector functions, such as antibody-dependent cellular cytotoxicity or complement-dependent cellular cytotoxicity as compared to IgG1 isotype monoclonal antibodies
- The potency of panitumumab is measured utilizing a _____ bioassay that _____
_____ This assay will be utilized for the commercial product release and replaced the _____ bioassay that was used during clinical trials. Comparability between the _____ and _____ bioassays was performed for panitumumab placed on long term stability as well as panitumumab placed under accelerated conditions. There is a noticeable decrease in the potency of panitumumab stored at 40°C that correlated with a decrease in potency using the _____ assay. The _____ bioassay is stability indicating, as it can detect changes in activity in panitumumab samples exposed to elevated temperature. Potency is defined as _____ with an approved specification of _____
- Amgen suggested broad acceptance criteria for a number of release and stability indicating assays, based upon the use of _____ tolerance intervals. The proposed specifications were narrowed to better reflect the panitumumab manufacturing and clinical experience, and based on knowledge gained from assay validation and product characterization. _____
- The Quality review generated a Discipline Review letter. The following items were included in the DR letter and were either resolved prior to licensure or were set as PMCs:
 1. The _____ potency bioassay acceptance criteria was set at _____. Please provide justification for these criteria based on clinical experience with panitumumab.
 2. In your August 24 and August 25, 2006 conversations with the agency regarding specifications, Amgen committed to setting internal action limits for specifications that are currently set outside of manufacturing experience. These limits should be defined and submitted along with the relevant actions to the BLA in a timely manner for FDA review and concurrence.
 3. The post approval stability protocol for drug product includes sterility testing at the _____ months stability time-points. Container closure integrity testing (CCIT) is a more meaningful assay to be used on stability. Amgen has previously used CCIT on DP containers from media fill studies. Amgen should revise the drug product stability protocol to include CCIT instead of sterility testing for the _____ month time-points.
 4. We remain concerned with the microbial controls for the _____ operations at _____ and the firm's ability to sufficiently mitigate microbial contamination to the product. We acknowledge that the firm has made _____

further assessment and some improvement after meeting with the agency. However, we still have concerns after viewing the new studies submitted.

Additional data, including

_____ have been requested and should be provided as soon as possible and no later than 5 business days from the date of this letter.

5. The _____

_____ could contribute to contamination risk. Because of the design of the facility and the process, the firm will need to demonstrate robust operational controls to address potential risks associated with these operations. Added assurance of _____ will be needed. In addition, a comprehensive assessment of the contamination risk of the product in relation to the facility and the process should be conducted, and a process improvement plan to the design in order to address weaknesses should be proposed where indicated.

6. Re-evaluation of drug substance and drug product specifications have been discussed. A plan to provide specification updates and re-assessment should be submitted to the BLA in a timely manner.

7.

8. As requested in the June 30, 2006 teleconference between Amgen and representatives of this Division, please provide data that address the impact of the change in Panitumumab diluent from the sodium acetate formulation buffer used in the animal toxicology studies to saline, as used in the clinical trials. Specifically, please provide data documenting that dilution of Panitumumab in the formulation buffer does not alter the in vivo distribution, toxicity, or biologic activity from that obtained when saline is used as the diluent. If Amgen has already submitted this information to the current BLA, please identify the amendment and module in the e-CTD where the data can be located; otherwise, please submit this information for review.

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

- Vectibix™ (panitumumab) is indicated as a single agent for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens
- Vectibix™ (panitumumab) drug product is currently provided as single use vials in 3 configurations: nominal 100mg of panitumumab per vial (5 mL of 20 mg/ml), nominal 200mg of panitumumab per vial (10 mL of 20 mg/ml), and nominal 400mg of panitumumab per vial (20 mL of 20 mg/ml),

- Vectibix vials should be stored under refrigeration at 2° to 8° C and protected from direct sunlight. Vectibix should not be shaken or frozen, The recommended expiration dating period for Vectibix™ vials is 24 months from date of manufacture when stored under these condition.
- The recommended dose of panitumumab is 6 mg/kg every 14 days.
- Panitumumab should be diluted in 100 ml of 0.9% sodium chloride for injection, USP, to a final concentration not to exceed 10 mg/mL prior to infusion. Diluted panitumumab solutions for infusion may be stored at controlled room temperature (20° to 25°C) for up to 6 hours or at 2° to 8°C for up to 24 hours.
- Panitumumab should be given by intravenous administration over approximately 60 minutes by an infusion pump through a peripheral line or indwelling catheter using a low protein binding 0.2 µm or 0.22 µm in-line filter. Doses higher than 1000mg should be administered over 90 minutes.
- Vectibix™ is packaged as a single use presentation. Formulation does not include preservatives so any unused portion remaining in the vial must be discarded.
- Panitumumab is ———
————— Immunohistochemical detection of EGFR protein expression should be evaluated for selection of patients appropriate for Vectibix™ therapy, inasmuch as these are the only patients studied and for whom benefit has been shown.

C. Basis for Approvability or Not-Approval Recommendation

- Panitumumab is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Panitumumab is manufactured consistently, leads to a safe and effective product, and should be approved for the proposed indication.
- Post-marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product.



III. Administrative

A. Reviewers' Signature

Product Reviewer: Chana Fuchs , Ph.D.

9/19/06.

Product Reviewer: Ruth Cordoba-Rodriguez, Ph.D.

9/19/06

B. Endorsement Block

Product Branch chief: Patrick Swann, Ph.D.

9/22/06

Product Acting Division Director: : Kathleen A. Clouse, Ph.D.

9/22/06

C. CC Block

Acting Office Director: Steven Kozlowski, M.D.

Division of Monoclonal Antibodies File/BLA STN 125147/0

109 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: ~~July 28, 2006~~

To: Administrative File, STN BL 125147/0

From: Janet Barletta, Ph.D. CDER/OC/DMPQ/TRFB, HFD-328 *JB 7/28/06*

Through: Brenda Uratani, Ph.D., Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328 *B Uratani 7/28/06*

Subject: Review Memo: To provide for the manufacture of Panitumumab drug product at
A separate review of the drug substance
will be provided by another reviewer in TFRB (Michele Clark-Stuart).

US License: 1080

Applicant: Amgen, Inc. ATO
Thousand Oaks, CA 91320

Facility: FEI: 2026154

Manufacturing Facility: /

Product: FEI: —
Panitumumab (Human monoclonal antibody to human epidermal growth factor receptor).

Indication: /

Due date: September 28, 2006

Recommendation: The submission is recommended for approval.

Review Summary

P.1. Description of the Composition of the Drug Product: Panitumumab is a sterile, preservative-free, colorless solution for IV infusion containing:

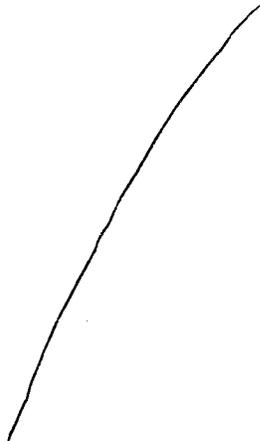
- Panitumumab
- NaCl
- sodium acetate trihydrate

P.2. Pharmaceutical Development: Panitumumab is a fully human monoclonal antibody of the immunoglobulin G2 subclass (IgG2) directed against the human epidermal growth factor receptor (EGFr). The drug substance is at a concentration (mg/mL) and the drug product formulation is a of the drug substance at a concentration of ng/ml with the same formulation buffer and excipients.

P.2.5. Microbiological Attributes:

Container-closure and package integrity: The container closure system consists of:

- 5, 10, and 20 mL Type 1 glass vial;
- stopper
- Aluminum seal) with flip-off dust cover.



as
als

SATISFACTORY

P.3. Manufacture:

P.3.1. Manufacturers: Amgen, Inc submitted this BLA to provide for Panitumumab drug substance manufacturing at Abgenix, Inc. (Fremont, CA) and drug product manufacturing at is responsible for manufacturing the drug product and limited release testing.

P.3.3. Description of the Manufacturing Process and Process Controls Building and facilities (floorplan, air quality, equipment locations):



10 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

BLA 125147/0 Amgen, Inc.

III. No additional inspectional follow-up items were identified.

Cc: HFD-328, Uratani
HFD- 328 Barletta
HFD-328, Clark-Stuart
HFD-123, Rawls
HFD-320, Famulare
HFD-328, TFRB Blue Files (STN)

Archived File: S:\archive\BLA\STN125147\0.rev.mem. 07-28-06.doc



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: May 23, 2006
To: Administrative File, STN 125147/0
From: Michelle Y. Clark-Stuart, MGA, MT (ASCP), CDER/OC/DMPQ TFRB, HFD-328
Through: Brenda Uratani, Ph.D., Acting Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328
Subject: Review Memo: Biological License Application (BLA): New BLA
US License: #1080
Applicant: Amgen, Inc.
Product: panitumumab
Indication:

Dosage: Sterile liquid vial for a single IV infusion (100mg/5ml; 200mg/10ml; 400mg/20ml)
Due date: Discipline review action (CMA Pilot 1 Program): June 17, 2006
First Action Due Date: September 28, 2006

*Mye's
8/3/06
Brenda Uratani
8/8/06*

Recommendation: The drug substance (DS) section of the application (3.2.S) application was reviewed from an equipment, facility, and microbiology quality perspective. The application is recommended for approval.

Review Summary

Amgen, Inc. submitted this BLA in support of the manufacturing of panitumumab, a recombinant, fully humanized monoclonal antibody (IgG2) directed against human epidermal growth factor (EGFr). Panitumumab is expressed as a recombinant protein in a Chinese Hamster Ovary (CHO) cell line. DS is manufactured at Amgen Fremont (AFR) in Fremont, CA (formerly Abgenix) and the drug product (DP) is manufactured at _____ Storage and testing of DS is performed at Amgen Thousand Oaks, CA (ATO).

The DS CMC sections of this electronic BLA were evaluated in this review for adequacy from an equipment, facility, and microbiology perspective. The sections evaluated included in part 2.3.S.2, 2.3.S.4, 2.3.S.6, and 2.3.S.7

Inspections of the facilities were conducted from May 30 – June 5, 2006 for AFR and June 7-8, 2006 for ATO by Michelle Y. Clark-Stuart, Ruth Cordoba-Rodriguez, and Chana Fuchs. A Form

STN 125147/0, Amgen, Inc.

FDA 483 was issued to the AFR facility on June 5, 2006. No Form FDA 483 was issued to the ATO facility.

Review Narrative

Drug Substance

Manufacturer – 3.2.S.2

The manufacturer of the drug substance is:

Amgen Fremont (formerly Abgenix, Inc. at time of submission)

6701 Kaiser Drive

Fremont, CA 94555

FEI pending (this is the first license application for a product from Abgenix)

Description of Manufacturing Process and Process Controls - 3.2.S.2.2

37 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Conclusion

- I. The drug substance section of the application is acceptable from an equipment, facility, and microbiology product quality perspective. The application is recommended for approval.
- II. The Drug Substance's Control of Source and Starting Materials of Biological Origin, Characterization, Batch Analyses, Justification of Specifications, Reference Standards, and Stability sections and/or subsections were not evaluated in this review.

In addition, the Drug Product's Composition, Batch Formula, Controls of Excipients, Reference Standards, and Stability sections and/or subsections were not evaluated in this review.

- III. Any items identified during the 5/30 – 6/5/06 and 6/7- 8/06 inspections at Amgen Fremont and Amgen Thousand Oaks are addressed in the corresponding Establishment Inspection Report (EIR).

Cc: HFD-328, Uratani
HFM-328, Clark-Stuart
HFD-328, Harper-Velazquez
HFD-328, TFRB Blue Files (STN 125147)