

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

APPLICATION NUMBER:

125147/0

**ADMINISTRATIVE DOCUMENTS AND
CORRESPONDENCE**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 125147/0 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

FDA Received Date: 3/29/06 Action Date: 9/28/06

HFM W7 Product and Proprietary names/dosage form: Panitumab (Vectibix)

Applicant: _____ Therapeutic Class: N/A

Indication(s) previously approved:
N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on a following fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy regimens

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 - No: Please check all that apply: Partial Waiver Deferred Completed
- NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children

- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

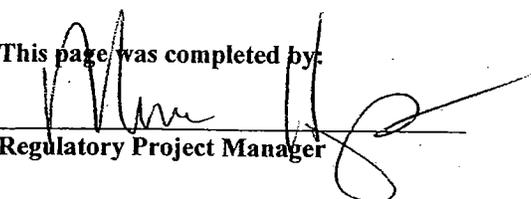
Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:


 Regulatory Project Manager

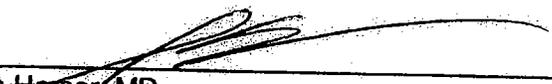
cc: NDA/BLA #
 HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03; revised 8-10-04 for RMS/BLA use)

1.3.3 Debarment Certification

Amgen hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Sean Harper, MD
Vice President, Global Regulatory Affairs and Safety

13 Feb 06
Date

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy.

(<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125147/0 Product: Panitumab Applicant: Amgen, Inc

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 5/10/04 Committee Recommendation (circle one) File RTF

RPM: Murphy 5/7/04
(signature/date)

Attachments:

Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

Part A - RPM

Part B - Product/CMC/Facility Reviewer(s) C. Fuchs m. Clark-shalt J. Belletta

Part C - Non-Clinical Pharmacology/Toxicology Reviewer(s): A. Pilero

Part D - Clinical (including Pharmacology, Efficacy, Safety, and Statistical)

Reviewers R. Gushi V. Koti H. Zhao

Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Form 356h completed	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> If foreign applicant, US Agent signature.	Y <input checked="" type="checkbox"/> N	N/A - not a foreign applicant
Comprehensive Table of Contents	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Debarment Certification with correct wording (see * below)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
User Fee Cover Sheet	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
User Fee payment received	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Financial certification &/or disclosure information	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Pediatric rule: study, waiver, or deferral	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Labeling:	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> PI -non-annotated	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> PI -annotated	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> PI (electronic)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> Medication Guide	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> Patient Insert	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> package and container	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> diluent	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> other components	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> established name (e.g. USAN)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> proprietary name (for review)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	Trademark + content and label under review as of 2/15/06.

* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge..."

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:	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> legible	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	

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Part A Page 2

Examples of Filing Issues	Yes?	If not, justification, action & status
<input type="checkbox"/> protocols for clinical trials present	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<input checked="" type="checkbox"/> Y N	
companion application received if a shared or divided manufacturing arrangement	Y <input checked="" type="checkbox"/> N	
if CMC supplement:		
<input type="checkbox"/> description and results of studies performed to evaluate the change	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> relevant validation protocols	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> list of relevant SOPs	<input checked="" type="checkbox"/> Y N	
if clinical supplement:		
<input type="checkbox"/> changes in labeling clearly highlighted	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> data to support all label changes	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	<input checked="" type="checkbox"/> Y N	
if electronic submission:		
<input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	<input checked="" type="checkbox"/> Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?

If yes, review committee informed? N/A

Does this submission relate to an outstanding PMC? no

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: ODAC
- Dates: 9/16/06

Possible ODAC presentation, tentatively scheduled for 9/16/06

Recommendation (circle one): File RTF

RPM Signature: [Signature]

Branch Chief concurrence: [Signature]

5/17/06

5/11/06

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Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Non-clinical overview [2.4]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Non-clinical summary [2.6]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Pharmacology	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Pharmacokinetics	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Toxicology	<input checked="" type="radio"/> Y <input type="radio"/> N	

CTD Module 4 Contents	Present?	If not, justification, action & status
Module Table of Contents [4.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Study Reports and related info. [4.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Pharmacology	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Pharmacokinetics	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Toxicology	<input checked="" type="radio"/> Y <input type="radio"/> N	
Literature references and copies [4.3]	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> protocol-specified (as opposed to a different, post-hoc analysis) and other critical statistical analyses included	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="radio"/> Y <input type="radio"/> N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	<input checked="" type="radio"/> Y <input type="radio"/> N	
for each non-clinical laboratory study, either a statement that the study was conducted in compliance with the good laboratory practice requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance	<input checked="" type="radio"/> Y <input type="radio"/> N	

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="checkbox"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="checkbox"/> N	
Clinical overview [2.5]	<input checked="" type="checkbox"/> N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="checkbox"/> N	No biopharmaceutical studies done.
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="checkbox"/> N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="checkbox"/> N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="checkbox"/> N	
Study Reports and related information [5.3]	<input checked="" type="checkbox"/> N	Not marketed product.
<input type="checkbox"/> Biopharmaceutic	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Pharmacokinetics (PK)	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Pharmacodynamic (PD)	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Postmarketing experience	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Case report forms	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> Individual patient listings (indexed by study)	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="checkbox"/> N	
Literature references and copies [5.4]	<input checked="" type="checkbox"/> N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> legible	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="checkbox"/> N	

Examples of Filing Issues	Yes?	If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records <input type="checkbox"/> protocols for clinical trials present <input type="checkbox"/> all electronic submission components usable	<input checked="" type="radio"/> Y N <input checked="" type="radio"/> Y N <input checked="" type="radio"/> Y N	
statement for each clinical investigation: <input type="checkbox"/> conducted in compliance with IRB requirements <input type="checkbox"/> conducted in compliance with requirements for informed consent	<input checked="" type="radio"/> Y N <input checked="" type="radio"/> Y N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	<input checked="" type="radio"/> Y N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	<input checked="" type="radio"/> Y N	Submitted for accelerated approval with confirmatory study submitted and accepted under SPA.
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	<input checked="" type="radio"/> Y N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y <input checked="" type="radio"/> N	Single therapeutic entity.
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	<input checked="" type="radio"/> Y N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	<input checked="" type="radio"/> Y N	
drug interaction studies communicated as during IND review as necessary are included	<input checked="" type="radio"/> Y N	None requested.
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	<input checked="" type="radio"/> Y N	
comprehensive analysis of safety data from all current world-wide knowledge of product	<input checked="" type="radio"/> Y N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	<input checked="" type="radio"/> Y <input type="radio"/> N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	<input checked="" type="radio"/> Y <input type="radio"/> N	
adequate characterization of product specificity or mode of action	<input checked="" type="radio"/> Y <input type="radio"/> N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	<input checked="" type="radio"/> Y <input type="radio"/> N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y <input checked="" type="radio"/> NR	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="radio"/> Y <input type="radio"/> N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
20020408	<input checked="" type="radio"/> Y	N	<input checked="" type="radio"/> Y	N	NR	<input checked="" type="radio"/> Y	N	<input checked="" type="radio"/> Y	N	NR
20030194	<input checked="" type="radio"/> Y	N	<input checked="" type="radio"/> Y	N	NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR
20030167	<input checked="" type="radio"/> Y	N	<input checked="" type="radio"/> Y	N	NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR
20030250	<input checked="" type="radio"/> Y	N	<input checked="" type="radio"/> Y	N	NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR
20025405	<input checked="" type="radio"/> Y	N	<input checked="" type="radio"/> Y	N	NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR
20025409 (I)	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR
20025409 (II)	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR
20030138	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR
20040116	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR
20040192	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR	<input checked="" type="radio"/> Y	N	Y	N	<input checked="" type="radio"/> NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None.

List of Clinical Studies (Contd.)

Study	Report	Disclosures	Datasets	BiMo Sites
20030251	Y	NR	Y	NR
2025408	Y	NR	Y	NR
20030110	Y	NR	Y	NR
20020374	Y	NR	Y	NR
20020375	Y	NR	Y	NR
20025404 (II)	Y	NR	Y	NR
20025404 (I)	Y	NR	Y	NR

Is clinical site(s) inspection (BiMo) needed?
Underway.

Is an Advisory Committee needed?
Unclear at this point.

Recommendation (circle one): File RTF

Reviewer: Ruthann M. Giusti ^{5/10/06} Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [Signature]
TC (signature/ date)
5/10/06

Division Director: _____
(signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y N	
Clinical overview [2.5]	<input checked="" type="radio"/> Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y N	
Study Reports and related information [5.3]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Biopharmaceutic	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Pharmacokinetics (PK)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Pharmacodynamic (PD)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Postmarketing experience	<input checked="" type="radio"/> Y N	→ Not applicable
<input type="checkbox"/> Case report forms	<input checked="" type="radio"/> Y N	→ Clinical
<input type="checkbox"/> Individual patient listings (indexed by study)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y N	
Literature references and copies [5.4]	<input checked="" type="radio"/> Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y N	

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Examples of Filing Issues	Yes?		If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	N	
<input type="checkbox"/> protocols for clinical trials present	Y	N	
<input type="checkbox"/> all electronic submission components usable	Y	N	
statement for each clinical investigation:			Clinical
<input type="checkbox"/> conducted in compliance with IRB requirements	Y	N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	Y	N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y	N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y	N	Clinical
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y	N	Clinical
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y	N	Not Applicable
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y	N	Clinical
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y	N	Clinical
drug interaction studies communicated as during IND review as necessary are included	Y	N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y	N	Clinical
comprehensive analysis of safety data from all current world-wide knowledge of product	Y	N	Clinical

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Part D Page 3

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y N	Statistics
adequate characterization of product specificity or mode of action	(Y) N	
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	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	Clinical
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y N	Clinical

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
20030251	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20040192	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20030138	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20020408	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20025405	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20030167	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20030250	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20025404	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20025408	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
20030110	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR

Y=yes; N=no; NR=not required

2004116 (Y)
 20020374 (Y)
 20025409 (Y)

(Y)
 (Y)
 (Y)

STN 125747

Product Panitumumab

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo):

None

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): File RTF

Reviewer: [Signature] 5/8/06 Type (circle one): Clinical Clin/Pharm Statistical

Concurrence:

Team Leader
Branch Chief: [Signature] 5/8/06
(signature/ date)

Division Director: [Signature] May 8, 2006
(signature/ date)

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125147/0 Product: panitumumab Applicant: Amgen/Immunex, Inc.

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date / / Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

____ Part A – RPM

Part B – Product/CMC/Facility Reviewer(s): Michelle Y. Clark-Stuart (lead), Janet Barletta

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____

____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____

- Memo of Filing Meeting

**APPEARS THIS WAY
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A

12 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Clinical overview [2.5]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	Y N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	Y N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Clinical Safety	Y N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y <input type="radio"/> N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Study Reports and related information [5.3]	Y N	
<input type="checkbox"/> Biopharmaceutic	Y N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
<input type="checkbox"/> Pharmacokinetics (PK)	Y N	
<input type="checkbox"/> Pharmacodynamic (PD)	Y N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Postmarketing experience	Y N	
<input type="checkbox"/> Case report forms	Y N	
<input type="checkbox"/> Individual patient listings (indexed by study)	Y N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of filing issues	Yes?		If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	N	
<input type="checkbox"/> protocols for clinical trials present	Y	N	
<input type="checkbox"/> all electronic submission components usable	Y	N	
statement for each clinical investigation:			
<input type="checkbox"/> conducted in compliance with IRB requirements	Y	N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	Y	N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y	N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y	N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y	N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y	N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y	N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y	N	
drug interaction studies communicated as during IND review as necessary are included	Y	N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y	N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y	N	

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	<input checked="" type="radio"/> Y	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	<input checked="" type="radio"/> Y	N	
adequate characterization of product specificity or mode of action	<input checked="" type="radio"/> Y	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	<input checked="" type="radio"/> Y	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	<input checked="" type="radio"/> Y	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="radio"/> Y	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
20020408	<input checked="" type="radio"/> Y	N	Y	N	NR	<input checked="" type="radio"/> Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Multiple horizontal lines for handwritten input.

Is clinical site(s) inspection (BiMo) needed?

Two horizontal lines for handwritten input.

Is an Advisory Committee needed?

Yes. It is not clear that clinical benefit has demonstrated or predicted.

Recommendation (circle one): File RTF

Reviewer: Kallappa Kori Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: _____
(signature/ date)

Division Director: Alaka Chakravarty
(signature/ date)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

The request for categorical exclusion review is located in Dr. Janet Barletta's facility review, page 12.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

This is a first cycle approval, no previous action letters were issued for 125174/0.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

The financial disclosure review is located in Dr. Ruthann Giusti's clinical review, page 32.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

No DSRCS review was completed for this file, 125147/0.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

The safety update review is located in Dr. Ruthann Giusti's clinical review, page 69-.

**APPEARS THIS WAY
ON ORIGINAL**

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Attachment to Form FDA 356h
Establishment Information for Panitumumab

Facility	Contact Person	Registration Number (CFN) / Labeler Code	Manufacturing Steps / Type of Testing
Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320	Wayne Pearl Vice President, Thousand Oaks Operations (805) 447-5436	2026154 / 055513	Drug substance stability and release testing Drug substance final release Drug substance staging and storage Drug product storage, release, and stability testing
Abgenix 6701 Kaiser Drive Fremont, CA 94555	Janice Castillo Vice President, Regulatory Affairs (510) 284-6934	Pending	Raw materials and components staging, storage, and testing Drug substance manufacture, staging, storage, stability (potency) and release testing Drug substance release for shipping Drug product release testing

1 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

STN BL 125147

6. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(805) 447-2518

3. PRODUCT NAME

panitumumab

6. USER FEE I.D. NUMBER

PD3006312

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 738(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

Senior Director, Regulatory Affairs

DATE

11/21/05



VENDOR NAME	CHECK NO.	CHECK DATE
FOOD & DRUG ADMINISTRATIO	01263728	11/23/05

Page 1 of 1

VEND. NO. 657863

CITIBANK DE

Check Amount:

\$767,400.00

DATE	INVOICE NUMBER	PAYMENT ADVISE	GROSS AMOUNT	DISCOUNT	NET AMOUNT
11/16/05	CR105403	ID#PD3006312; BLA#125147-0	767,400.00		767,400.00
TOTALS			767,400.00		767,400.00

Alt. Payee
657863

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C/O MELLON BANK FOR FDA LOCKBOX 360909
PITTSBURGH PA 15262-0001



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THOUSAND OAKS CA 91320-1789

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NEWCASTLE DE 19720

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1263728	11/23/05

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ACTION PACKAGE CHECKLIST

Application Information

BLA # 125147/0 NDA #	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Panitumumab Established Name: Vectibix Dosage Form: 6mg/kg IV over 60 minutes		Applicant: Amgen, Incorporated
RPM: Monica Hughes, M.S.		HFD-107 Phone # 301-796-2320
NDAs only: Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs only: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> If no listed drug, check here, and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		September 28, 2006
❖ Action Goal Date (optional)		
❖ Actions		
• Proposed action		X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		X None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input type="checkbox"/> Requested in AP letter X Received and reviewed

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
Chemical classification (new NDAs only):	
NDAs, BLAs and Supplements:	
<input type="checkbox"/> Fast Track	
<input type="checkbox"/> Rolling Review	
<input checked="" type="checkbox"/> CMA Pilot 1	
<input type="checkbox"/> CMA Pilot 2	
<input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H	BLAs: Subpart E
<input type="checkbox"/> Accelerated approval (21 CFR 314.510)	<input checked="" type="checkbox"/> Accelerated approval (21 CFR 601.41)
<input type="checkbox"/> Restricted distribution (21 CFR 314.520)	<input type="checkbox"/> Restricted distribution (21 CFR 601.42)
Subpart I	Subpart H
<input type="checkbox"/> Approval based on animal studies	<input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements:	
<input type="checkbox"/> OTC drug	
Other:	
Other comments:	

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
• OC clearance for approval (<i>file communication in Administrative Documents section</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? 	<p>X No <input type="checkbox"/> Yes</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:</p> <p><input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p> <p><input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p> <p><input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p>
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	<p>Not Applicable</p>
<ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p>
<ul style="list-style-type: none"> • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of</p>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
	<input type="checkbox"/> Yes <input type="checkbox"/> No

this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

Summary Reviews

❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	September 26, 2006
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	September 27, 2006

Labeling

❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	September 14, 2006
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	September 20, 2006
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	March 28, 2006
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Erbix: Supplement approved on 3-1-06
❖ Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	Not Applicable
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	Not Applicable
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	September 20, 2006 September 20, 2006
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
<ul style="list-style-type: none"> • Labeling reviews that address only carton and container labels 	
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS 9/5/06 <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 9/8/06 <input checked="" type="checkbox"/> Other reviews 9/20/06 (M. Hughes) <input type="checkbox"/> Memos of Mtgs

Administrative Documents

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting/ADRA) (indicate date of each review)	May 10, 2006
❖ NDA approvals only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included
❖ AIP-related documents	Not Applicable
<ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	
❖ Pediatric Page	May 7, 2006
Debarment certification (original applications only): verified that qualifying language was not used in certification & certifications from foreign applicants are cosigned by US agent. (Include certification.)	X Verified

❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
• Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)	September 20, 2006
• Incoming submission documenting commitment	August 31, 2006 September 8, 2006
❖ Outgoing correspondence (letters, emails, faxes, telecons)	January 11, 2006 March 8, 2006 April 27, 2006 May 24, 2006 June 9, 2006 June 14, 2006 June 15, 2006 August 11, 2006 August 29, 2006 August 31, 2006 September 1, 2006 September 15, 2006
❖ Internal memoranda, telecons, email, etc.	January 10, 2006 January 12, 2006 February 2, 2006 March 9, 2006 March 29, 2006 April 5, 2006 April 28, 2006 June 29, 2006 June 30, 2006 July 14, 2006 July 21, 2006 July 28, 2006 August 4, 2006
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	September 12, 2006
• Pre-NDA/BLA meeting (<i>indicate date</i>)	June 21, 2006 June 23, 2006 December 13, 2005
• EOP2 meeting (<i>indicate date</i>)	July 9, 2003 July 18, 2003
• Other (e.g., EOP2a, CMC pilot programs)	December 30, 2004 October 5, 2006 October 12, 2005 May 15, 2006
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	September 22, 2006
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	
❖ BLAs: Product subject to lot release (APs only)?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

❖ Environmental Assessment (original and supplemental applications) (check one)	
• <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(all original applications and all efficacy supplements that could increase the patient population)	In facility review (Michelle Clark-Stuart): page 34
• <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
• <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ NDAs: Microbiology reviews (validation of sterilization & product sterility) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not a parenteral product
❖ NDAs: Facilities inspection (include EER printout)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ BLAs: Facility-Related Documents	
• Facility review (<i>indicate date(s)</i>)	July 28, 2006 August 8, 2006
• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date, must be completed within 60 days prior to AP</i>)	X Requested 9/7/06 X Accepted 9/11/06 <input type="checkbox"/> Hold <input type="checkbox"/> Cleared from hold

Nonclinical Information

❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	September 21, 2006
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	
Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	
❖ ECAC/CAC report/memo of meeting	

Clinical Information

❖ Clinical review(s) (<i>indicate date for each review</i>)	September 26, 2006
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	In clinical review pages: 32
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	Not Applicable
❖ Microbiology (efficacy) review(s) (<i>indicate date of each review</i>)	X Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	In clinical review pages: 69
❖ Risk Management Plan review(s) (including ODS)-(indicate location/date if incorporated into another review)	X None
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	X Not needed
❖ Clinical Inspection Review Summary (DSI)	<input type="checkbox"/> None requested
• Clinical studies (<i>include copies of DSI letters to investigators</i>)	August 4, 2006
• Bioequivalence studies (<i>include copies of DSI letters to investigators</i>)	
❖ Statistical review(s) (<i>indicate date of each review</i>)	<input type="checkbox"/> None 9/12/06 & 9/14/06
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/20/06

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Comments:

Applicant: Amgen, Inc.

STN: 125147/0

Product:

Panitumumab (Vectibix)

Indication / manufacturer's change:

Vectibix is indicated for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Approval:

- Summary Basis For Approval (SBA) included
- Memo of SBA equivalent reviews included

- Refusal to File: Memo included
- Denial of application / supplement: Memo included

RECOMMENDATION BASIS

- Review of Documents listed on Licensed Action Recommendation Report
- Inspection of establishment Inspection report included
- BiMo inspections completed BiMo report included
- Review of protocols for lot no.(s) _____
- Test Results for lot no.(s) _____
- Review of Environmental Assessment FONSI included Categorical Exclusion
- Review of labeling Date completed 9-26-06 None needed

CLEARANCE - PRODUCT RELEASE BRANCH

- CBER Lot release not required
- Lot no.(s) in support - not for release _____
- Lot no.(s) for release _____
- Director, Product Release Branch _____

CLEARANCE - REVIEW

Review Committee Chairperson: [Signature] Date: 9/26/2006

Product Office's Responsible Division Director(s)*: [Signature] Date: 9-26-2006

DMPQ Division Director*: [Signature] Date: 9/26/2006

* If Product Office or DMPQ Review is conducted

CLEARANCE - APPLICATION DIVISION

- Compliance status checked Acceptable Hold Date: 9/11/06
- Compliance status check Not Required Cleared from Hold Date: _____

Regulatory Project Manager (RPM) [Signature] Date: 9/27/06

Responsible Division Director [Signature] Date: 9/27/06

(where product is submitted, e.g., application division or DMPQ)

LICENSING ACTION RECOMMENDATION

Applicant: Amgen, Inc. STN: 125147/0

Product: Panitumumab (Vectibix)

Indication / manufacturer's change:
Vectibix is indicated for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

- Approval:
 - Summary Basis For Approval (SBA) included
 - Memo of SBA equivalent reviews included
- Refusal to File: Memo included
- Denial of application / supplement: Memo included

RECOMMENDATION BASIS

- Review of Documents listed on Licensed Action Recommendation Report
- Inspection of establishment Inspection report included
- BIMO inspections completed BIMO report included
- Review of protocols for lot no.(s) _____
- Test Results for lot no.(s) _____
- Review of Environmental Assessment FONSI included Categorical Exclusion
- Review of labeling Date completed 9-26-06 None needed

CLEARANCE - PRODUCT RELEASE BRANCH

- CBER Lot release not required
- Lot no.(s) in support - not for release _____
- Lot no.(s) for release _____
- Director, Product Release Branch _____

CLEARANCE - REVIEW

Review Committee Chairperson: [Signature] Date: 9/26/2006

Product Office's Responsible Division Director(s)*: Patrick Swann for K. CLOUSE Date: 9/27/2006

DMPQ Division Director*: [Signature] Date: 9/26/2006

* If Product Office or DMPQ Review is conducted

CLEARANCE - APPLICATION DIVISION

- Compliance status checked Acceptable Hold Date: _____
- Cleared from Hold Date: _____
- Compliance status check Not Required

Regulatory Project Manager (RPM) _____ Date: _____

Responsible Division Director (where product is submitted, e.g., application division or DMPQ) _____ Date: _____

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
OFFICE OF ONCOLOGY DRUG PRODUCTS
DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS

White Oak Office Complex – Building 22
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
FAX #: 301-796-9849

FACSIMILE TRANSMISSION RECORD

31

TOTAL NUMBER OF PAGES: _____ (Including Cover Page)

FAX TO: Alessandra Cesano, M.D., and/or Mary Scott, Ph.D., MBA, at Amgen, Inc.

Facsimile Telephone No. (805) 480-1330 Voice Telephone No. _____

FROM: Monica Hughes, M.S., Regulatory Project Manager

Facsimile Telephone No. 301-796-9849 Voice Telephone No. 301-796-1371

DATE: September 27, 2006 TIME: _____

MESSAGE: Alessandra or Mary,

Attached is a copy of the approval letter, approved package insert, and approved carton and vial labeling for the Panitumumab (Vectibix) BLA 125147/0.

Please send written confirmation via E-mail to monica.hughes@fda.hhs.gov or via facsimile as soon as possible to confirm receipt.

Thank you. Monica Hughes, M.S., Regulatory Project Manager

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Hughes, Monica L

From: Scott, Mary [mascott@amgen.com]
Sent: Wednesday, September 27, 2006 3:29 PM
To: Hughes, Monica L
Subject: Confirmation of receipt
Attachments: emfinfo.txt

This is to confirm I am in receipt of your 31 page fax dated 27 September!

Mary Celine Scott, PhD, MBA
Senior Manager, Regulatory Affairs
Amgen
Phone (805) 447-3741
Fax (805) 480-1330
Pager (805) 359-3381

C

6 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

Memorandum

Date: September 20, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: Vectibix (Panitumumab) Carton and Vial Labeling Review

Amgen originally submitted draft carton and vial labeling to IND 8382 on February 1 and 15, 2006, along with their request for a tradename review for Vectibix. The tradename review request along with the carton and vial labeling and package insert were sent to OSE/DMETS, DDMAC, and the OPS/DMA review staff for comments, in addition to review comments from DBOP/OODP. On June 16, 2006, we issued a letter to Amgen tentatively accepting the tradename Vectibix and incorporating comments regarding labeling from OSE/DMETS and OPS/DMA. In this letter we requested that they re-submit their request for tradename review 90 days prior to the anticipated PDUFA action date for the application along with revised carton and vial labeling that incorporated the following comments:

GENERAL COMMENTS:

1. The concentrations expressed on the container labels and carton labeling are inconsistent with what is expressed in the insert labeling. In the insert labeling, all three strengths are stated to have a concentration of 20 mg/mL. However, in the container labels and carton labeling, the Revise the
labels and labeling to accurately reflect the actual contents of each vial.
2. The strength is expressed in terms of total 'mg per vial' without reference to a corresponding milliliter amount. Post-marketing evidence has demonstrated that omitting this information may lead to calculation errors. Thus, we request that you revise the expression of strength to include the total milligrams and milliliter. For example:
400 mg/20 mL
(20 mg/mL)
3. Since each vial is a single use vial, include a statement that indicates that the unused portion should be discarded. Otherwise, unused portions may be retained for future doses.
4. Ensure that the established name is as prominent as the proprietary name per 21 CFR 610.62 (b).
5. The strength is displayed more than once in its current presentation. Revise the labels and labeling so that the strength is prominently displayed only once.

CONTAINER LABEL:

6. See GENERAL COMMENTS.
7. The — color contrasted with the — (200 mg/vial) background color is difficult to read (see below in B-3). Revise the background color to improve readability of the strength, unit designations, and NDC number or use a darker font color so that it is contrasted with the color used for the numbers and letters. Also, please ensure that the new colors can be clearly differentiated from the 100 mg/vial and 400 mg/vial strengths.
8. The colors use to designate the 200 mg/vial and 400 mg/vial appear to be similar to one another when compared side-by-side. We believe that the similar colors have the potential to cause selection errors as the strength may be confused. We recommend revising the colors so that they are clearly differentiated from one another and from the 100 mg/vial strength.
9. The carton/package labeling should note the preservative used and its concentration; if no preservative is used and the absence of a preservative is a safety factor, then the words "no preservative" should be noted.
10. Please note that when the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit visual inspection of the contents (21 CFR 610.60).

CARTON LABELING:

11. See GENERAL COMMENTS and comments 7 and 8.
12. A — is present which interferes with the readability of the name. Reduce the prominence of — or remove it from the labeling.

INSERT LABELING:

13. See comment # 1.

We request that you resubmit all revised labels and labeling to BL STN 125147/0 at least 90 days ahead of the anticipated approval of the BLA. Please note, these are preliminary comments and additional comments may follow a comprehensive review of all Panitumumab labeling.

Amgen responded on June 27, 2006, with their final request for approval of the tradename, Vectibix and their revised carton and vial labeling. All information was forwarded to OSE/DMETS, DDMAC, and OPS/DMA for comments, in addition to being reviewed in DBOP/OODP. DBOP/OODP issued a letter on September 15, 2006, accepting Vectibix as the tradename along with the following additional carton and vial labeling comments:

Package Insert Comments:

1. Regarding the use of Vectibix™ and Panitumumab in the package insert, please ensure that it complies with 21 CFR 201.10(g)(1).

Vial Comments:

2. Please confirm that the vial with the labeling attached conforms to 21 CFR 610.60(e) to allow for visual inspection of the contents of the vial.
3. _____ does not appear on vial, however, it was on the original vial labeling submitted on February 15, 2006, please clarify why it was removed and insert in place of _____
4. "Panitumumab" does not comply with 21CFR 210.10(g)(2) which outlines the prominence regulations. Please increase the prominence with respect to Vectibix™.
5. We recommend that you use the layout of the original vial, submitted on February 15, 2006, as it was easier to read. To improve readability we recommend the _____ use bold font. It does appear that the insertion of this _____ on the vial has changed the layout and readability of the vial. We recommend decreasing the size of the _____ to ensure readability of the vial.
6. We recommend, per 21 CFR 610.62(b), that a greater color contrast between the background color and font color be utilized on the 400mg vial, as it is difficult to read with the current color selections.

Carton Comments:

7.

8. We recommend that the statement _____ appear on the front of the carton.
9. It is recommended _____ " also be printed on the back panel of the carton.
10. It is recommended the statements _____ be printed on the back panel of the carton. Please revise _____ for consistency with " _____ " on the front panel of the carton.
11. We recommend per 21 CFR 610.62(b) that a greater color contrast between the background color and font color be utilized on the 400mg carton, as it is difficult to read with the current color selections.
12. We recommend that " _____ , on the front of the carton, be in bold font.

Date ,9/18/2006

Time 5 :40 pm

FDA participants: Chana Fuchs

Amgen participants: Jennifer Mercer

Telephone no: 805-447-1285

Telecon notes:

I called Amgen and left a message on Jennifer's voicemail re — testing for reference standard. In the BLA, — testing is not included for future ref stds although it was done for the current and previous ref stds. However, on our inspection at — — I received a list of all testing and it clearly identifies — testing for the CHO — commercial ref std.

Asked her to get back to me at my number.

J 9/18/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125174/0

SEP 15 2006

Amgen, Incorporated
Attention: Alessandra Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Cesano:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We refer to your February 1 and 15, 2006, submissions which contained your proposed proprietary name, Vectibix™, and its associated carton and vial labeling and to our June 16, 2006, letter in which we tentatively accepted your proprietary name, Vectibix™, and which also contained suggested revisions in which we attempted to focus on safety issues relating to possible medication errors.

We have reviewed your June 27, 2006, submission regarding your proprietary name for Panitumumab in consultation CDER's Office of Drug Safety and the Division of Drug Marketing, Advertising, and Communication's, and have concluded that the proprietary name "Vectibix™" is acceptable at this time under 21 CFR Part 201.

In addition, we have reviewed your revised Vectibix™ carton and vial labeling and we have the following additional comments:

Package Insert Comments:

1. Regarding the use of Vectibix™ and Panitumumab in the package insert, please ensure that it complies with 21 CFR 201.10(g)(1).

Vial Comments:

2. Please confirm that the vial with the labeling attached conforms to 21 CFR 610.60(e) to allow for visual inspection of the contents of the vial.
3. _____ does not appear on vial, however, it was on the original vial labeling submitted on February 15, 2006, please clarify why it was removed and insert in place of _____

4. "Panitumumab" does not comply with 21CFR 210.10(g)(2) which outlines the prominence regulations. Please increase the prominence with respect to Vectibix™.
5. We recommend that you use the layout of the original vial, submitted on February 15, 2006, as it was easier to read. To improve readability we recommend the _____ "Vial" use bold font. It does appear that the insertion of this _____ on the vial has changed the layout and readability of the vial. We recommend decreasing the size of the _____ to ensure readability of the vial.
6. We recommend, per 21 CFR 610.62(b), that a greater color contrast between the background color and font color be utilized on the 400mg vial, as it is difficult to read with the current color selections.

Carton Comments:

7.



or

8. We recommend that the statement _____ appear on the front of the carton.
9. It is recommended the _____ also be printed on the back panel of the carton.
10. It is recommended the statements _____ also be printed on the back panel of the carton. Please revise _____ for consistency with "_____" on the front panel of the carton.
11. We recommend per 21 CFR 610.62(b) that a greater color contrast between the background color and font color be utilized on the 400mg carton, as it is difficult to read with the current color selections.
12. We recommend that _____, on the front of the carton, be in bold font.

13. In our June 16, 2006, letter we requested that you reduce the size of _____ to improve readability of the name. We note that you moved the location _____, however, it is not clear if you reduced the size. In addition, the _____ did not appear on the original vial labeling submitted on February 15, 2006. It does appear that the insertion of this _____ on the vial has changed the layout and readability of the vial. We recommend decreasing the size of the _____ or removing it to ensure readability of the vial.
14. We recommend deleting the following line that appears on the 100mg, 200mg, and 400mg cartons: _____ as this statement may be confusing and the information appears on the label in other locations.

We request that you resubmit all revised carton and vial labels to BL STN 125147/0 by September 20, 2006, to allow for a final review.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, M.S., at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 14, 2006
From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP
Subject: 125147/0: Labeling Revisions

The attached contains FDA suggested revisions to the package insert that was forwarded to Amgen, Inc.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 12, 2006 /
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: OSE Safety Conference for 125147/0

The OSE (Office of Surveillance and Epidemiology) safety conference meeting was an internal team meeting with the DBOP (Division of Biological Oncology Products) to discuss Amgen's Vectibix™ which is indicated for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

FDA Attendees included:

Monica Hughes
Ruthann Giusti
Patricia Keegan
Kallapa Koti
Kaushikkumar Shastri
Richard Pazdur
Karen Weiss
Karen Jones
Anne Pilaro
Angela Men
Hong Zhao
Chana Fuchs
Jennifer Rouine
Sam Chan
Mark Avigan
Francis Kalush

The OSE safety conference began with members of the review team providing DDRE (Division of Drug Risk Evaluation) an overview of the application and of the monoclonal antibody itself.

DDRE asked about the status of the confirmatory trial and if we were concerned with a high amount of "off-label" use. DBOP stated the confirmatory trial is for 2nd line mCRC and is currently ongoing. DBOP does not expect extensive off-label use following approval.

DBOP stated that some of the safety information is indicative of a class effect for anti-EGFR antibodies and tyrosine kinase inhibitors that affect this downstream signaling pathway (Tarceva, Iressa). For example, there is a high amount of mucocutaneous toxicity (skin rash, acniform, erythema, dermatitis, skin fissures, paronychia, etc.). DDRE inquired about patient management and DBOP replied that standard medical management consisted of withholding the

drug and noted that there were 2 fatal events regarding skin toxicity reported. DBOP stated that a systematic approach to the medical treatment (use of topical antibiotics) was not studied nor collected during the pre-marketing trials, however there is a study to be conducted as a PMC to evaluate medical management of skin toxicities. DBOP requested that DDRE track all skin-related (skin, eye, GI mucosal) toxicities.

DBOP also noted pulmonary toxicity (pulmonary fibrosis, interstitial lung disease) and diarrhea as adverse events for which patients were treated symptomatically and for which doses were withheld as other adverse events resulting in termination of drug dosing. DDRE noted that ILD may be an issue for long term use patients, however as DBOP noted, the indicated population will be taking the drug for a median of 8 weeks, and few patients are expected to live more than 6 months.

DDRE asked if DBOP expected a synergistic increase in diarrhea with Irinotecan or 5FU. DBOP responded yes, and a warning has been incorporated into the panitumumab label.

DBOP mentioned electrolyte depletion (hypomagnesemia, hypocalcemia, hypokalemia), and cardiotoxicity as other adverse events of concern with antibodies directed against EGFR. DBOP noted that Erbitux (anti-EGFR antibody) was associated with sudden deaths (presumed cardiotoxicity) in the head and neck cancer clinical trials; there was not a lot of electrolyte monitoring conducted in this study so it was not possible to differentiate between direct cardiac effects and electrolyte changes leading to arrhythmia and sudden death. While electrolyte depletion was seen in trials of panitumumab, sudden death has not been reported.

DBOP noted that Erbitux has a black box warning for infusion reactions, presently the panitumumab package insert does not. However, additional discussion during this conference and subsequent labeling meeting led to the addition of a black box warning for infusional toxicity in the panitumumab label.

DBOP stated that as a PMC, —

will be requested.

DBOP requested that DDRE provide surveillance assistance for the following adverse reactions regarding panitumumab: infusional toxicity, pulmonary toxicity, cardiotoxicity (sudden deaths and arrhythmias), and all skin related toxicities, especially those related to failure to dose modification recommendations (pushing the dose).

DDRE asked DBOP to request that PSURs contain the estimated number of all patients receiving panitumumab across all cancer subtypes. DDRE can track the number of prescriptions written but also wanted to know total patient exposure. DBOP will request Amgen clarify and provide estimates in PSURs.

Safety conference adjourned and the review team moved on to revise labeling.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 12, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: Labeling Meeting for 125147/0

Forth team labeling meeting to discuss Amgen's proposed package insert for Vectibix™ which is indicated for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

FDA Attendees included:

Monica Hughes
Ruthann Giusti
Patricia Keegan
Kallapa Koti
Kaushikkumar Shastri
Richard Pazdur
Karen Weiss
Karen Jones
Anne Pilaro
Angela Men
Hong Zhao
Chana Fuchs
Francis Kalush

Team agreed to call Amgen to let them know that in our proposed revisions, we have included 2 black box warnings. We called Dr. Mary Scott at the conclusion of this meeting to let her know and indicated we still had some additional revisions to make to the PI and would send our proposed revisions as soon as possible, prior to the standing teleconference on Friday.

Team agreed to continue making the remaining revisions via email prior to sending it to Amgen for comments later in the week.

Hughes, Monica L

From: Barletta, Janet
Sent: Monday, September 11, 2006 1:54 PM
To: Hughes, Monica L
Subject: FW: Compliance Checks for _____ ,25147-0

Monica,
Below are the compliance checks for _____ (which you requested) regarding BLA 125147-0.
Please let me know if you need anything else.

Thanks,
Janet

Janet Barletta, Ph.D.
Interdisciplinary Scientist (Microbiologist)
Office of Compliance/Therapeutic Facilities Review Branch
RKW2, Rm 1015, HFD-328
5515 Security Lane
Rockville, MD 20852-1448
Telephone (301) 443-5189
FAX (301) 443-5245

From: Merritt, Babette A
Sent: Friday, September 08, 2006 10:21 AM
To: Barletta, Janet
cc: Rivera Martinez, Edwin; Cruz, Concepcion; Hovt, Colleen; Ferguson, Shimette D; Kiel, Hea S
Subject: RE: Compliance Checks for _____

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the compliance check request below. There are no pending or ongoing compliance actions to prevent approval at this time.

The following is the current status:

<i>Manufacturer Status</i>	<i>FEI #</i>	<i>Last EI Date</i>	<i>Profile</i>
_____	_____	11/24/04	CTL
AC (CFN# _____)	NAI 1/12/05		
_____	_____	3/10/06	CHG,CTR,POW,SUP,SVT,TCT,TTR,
AC (CFN# _____)	NAI 3/21/06		TDP,TCM,SVS,SVL,SNI,OIN,LIQ,CSG

*Have a wonderful day,
Babette*

*Babette Angela Merritt
Consumer Safety Officer*

From: Barletta, Janet
Sent: Friday, September 08, 2006 9:19 AM
To: CDER-TB-EER
Subject: Compliance Checks

Please provide compliance checks of the following facilities:

1.

CFN - /

2.

CFN /

3

CFN: /

Thank you,

Janet Barletta, Ph.D.
Interdisciplinary Scientist (Microbiologist)
Office of Compliance/Therapeutic Facilities Review Branch
RKW2, Rm 1015, HFD-328
5515 Security Lane
Rockville, MD 20852-1448
Telephone (301) 443-5189
FAX (301) 443-5245

16 Page(s) Withheld

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

 ✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

hes, Monica L

From: Hughes, Monica L
Sent: Thursday, September 07, 2006 9:16 AM
To: Uratani, Brenda W; Barletta, Janet; Harper Velazquez, Tia M
Cc: Keegan, Patricia; Jones, Karen
Subject: RE: Establishment Evaluation Request for Panitumumab 125147/0
Importance: High
Follow Up Flag: Follow up
Due By: Tuesday, September 12, 2006 9:00 AM
Flag Status: Flagged
Attachments: 356h.pdf

Thank you Brenda and Janet,

I believe the only outstanding issue is to request an establishment evaluation request for the Panitumumab approval on 9/28/06.

I am hoping it is possible to have the compliance check completed as soon as possible, no later than 9-12-06.

I am attaching all the establishment information. Please let me know if you need additional information.

Thank you,

a

From: Uratani, Brenda W
Sent: Wednesday, September 06, 2006 4:14 PM
To: Keegan, Patricia; Hughes, Monica L
Cc: Fuchs, Chana; Barletta, Janet; Buhay, Nicholas
Subject: FW: Panitumumab BLA 125147-00_Response to Discipline Review Letter_It em 4 and 5

Hi Pat and Monica,

The Amgen response, regarding their corrective actions taken for the deficiencies uncovered during inspection, is acceptable. The implementation of the corrections will be evaluated in the next inspection, most likely by an expedited surveillance inspection post-approval (i.e., we will request for an expedite inspection sooner than the normal 2 years timeframe). Therefore, as far as the GMP compliance status for commercial manufacturing is concerned, TFRB found it acceptable for the approval of this BLA.

Thank you for your patience.

Brenda

From: Mercer, Jennifer [mailto:jmerc@amgen.com]
Sent: Wednesday, September 06, 2006 3:15 PM

9/7/2006

To: Hughes, Monica L; Fuchs, Chana; Uratani, Brenda W

Corandi, Anthony'

Subject: Panitumumab BLA 125147-00_Response to Discipline Review Letter_Item 4 and 5

Dear Brenda,

As discussed at the teleconference held on 31 August 2006 and in response to the Quality Discipline Review letter dated 28 August 2006, the response to Item 4 and 5 is provided in this email for your review. If you have any questions, please feel free to give me a call at 805-447-1285.

Monica – the remaining CMC responses will be emailed to you on Friday, Sept 8.

Best Regards,

Jennifer Mercer
Amgen
Regulatory Affairs, CMC



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 31, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: Labeling Meeting for 125147/0.

Forth team labeling meeting to discuss Amgen's proposed package insert for Vectibix™ which is indicated for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

FDA Attendees included:
Monica Hughes
Ruthann Giusti
Patricia Keegan
Kallapa Koti
Kaushikkumar Shastri

Team agreed to continue making the remaining revisions via email prior to sending it to Amgen for comments later today.

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: September 1, 2006

From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP

Subject: 125147/0: Labeling Revisions

The attached contains FDA suggested revisions to the package insert that was forwarded to Amgen, Inc. These additional revisions were inadvertently left off of the 8-31-06 FDA comments forwarded to Amgen. These additional revisions were discussed during the 9-1-06 teleconference.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 31, 2006
From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP
Subject: 125147/0: Labeling Revisions

The attached contains FDA suggested revisions to the package insert that was forwarded to Amgen, Inc.

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL



Our STN: BL 125147/0

AUG 29 2006

Amgen, Incorporated
Attention: Alessandra Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Cesano:

Please refer to your biologics license application (BLA) for Panitumumab, submitted under the Continuous Marketing Application (CMA)-Pilot 1 program and to your February 24, 2006, reviewable unit (RU) for the Chemistry, Manufacturing, and Controls section of your BLA.

We have completed our review of this RU and have identified the following potential deficiencies:

1. The _____ bioassay acceptance criteria was set at _____ of the reference standard. 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 video 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 manual 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. This information should be provided as soon as possible to allow for a timely review by the agency.
6. Re-evaluation of drug substance and drug product specifications has 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.

We are providing these comments to you before we complete our review of your entire application to give you preliminary notice of issues that we have identified. These comments are being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and do not reflect a final decision on the information reviewed. Issues may be added, deleted, expanded upon, or modified as we review the complete application.

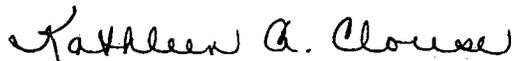
Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, M.S., at (301) 796-2320.

Sincerely,



Kathleen A. Clouse, Ph.D.
Acting Director
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Sciences
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 29, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: Labeling Meeting for 125147/0

Third team labeling meeting to discuss Amgen's proposed package insert for Vectibix™ which is indicated for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

FDA Attendees included:

Monica Hughes
Ruthann Giusti
Anne Pilaro
Angela Men
Hong Zhao
Patricia Keegan
Jennifer Rouine
Kallapa Koti
Kaushikkumar Shastri
Nina Chace
Francis Kalush
Patricia Love

Team agreed to continue making the remaining revisions via email and set up another brief meeting for the clinical team prior to sending it to Amgen for comments.

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2 Page(s) Withheld

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§ 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

Memorandum

Date: August 11, 2006

From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP

Subject: 125147/0: Labeling Revisions

The attached contains FDA suggested revisions to the package insert that was forwarded to Amgen, Inc.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

e-mailed questions

From: Fuchs, Chana
Sent: Thursday, August 10, 2006 11:40 PM
To: 'Mercer, Jennifer'
Subject: Panitumumab - clarification requested

cf 9/18/06

Hi Jennifer

I'm looking at the _____ information in front of me.
My notes have it that 2 lots have been _____, step.
Based on the numbers, it easy to see that they were lots 5648/5648-01 and 1953-01,
I cannot find a description of _____ of these lots in the BLA - just know so because of the
inspection. Is it somewhere in the BLA?

Additionally, I also cannot find a 2546 -01 part for the 2546 lot at the moment. The batch record
in 32s44 is only for 2546 _____ (based on the number). I think I remember from the
inspection at abgenix that this _____ lot was put on stability (i.e. it exists somewhere).

I would appreciate any clarification you can provide on both points,

Thanks,
Chana.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 4, 2006 *ml*

From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP

Subject: 125147/0: Standing Weekly Teleconference

FDA Attendees:

Monica Hughes
Ruthann Giusti

Amgen Attendees:

Julie Lepin
Mike Wolf
Jennifer Mercer
Sophie Visonneau
Mary Celine Scott

Discussion: FDA asked Amgen how the toxicity grades were assigned in the 20020408 trial for those toxicities for which the preferred term and the CTCAE term may not correspond.

Amgen stated that for those instances Amgen went back to the verbatim to assign non corresponding events. For example, for some patients disease progression would be more appropriate than toxicity. FDA recommended removing mCRC from the table.

Amgen stated that the confirmatory trial has enrolled 10 patients as of the end of this week, and confirmed that all patients will receive the — product.

APPEARS THIS WAY
ON ORIGINAL

Table 1. Per-Patient Incidence of Adverse Reactions Occurring in $\geq 5\%$ of Patients with a Between Group Difference of $\geq 5\%$

Body System	Patients Treated With Vectibix™ plus BSC (n = 229)				BSC Alone (n = 234)	
	Grades 1-4	Grade 3	Grade 4	Grade 1-4	Grade 3	Grade 4
Preferred Term ¹	% of Patients					
Body as a Whole						
Fatigue	55 (24)	10 (4)	0 (0)	34 (15)	7 (3)	0 (0)
General deterioration	23 (10)	11 (5)	5 (2)	8 (3)	2 (1)	3 (1)
Growth of eyelashes	12 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Colorectal Cancer Metastatic	29 (13)			17 (7)		
Infusional toxicity	3 (1)	0 (0)	0 (0)	na	na	Na
Digestive						
Abdominal Pain	52(23)	17 (7)	0 (0)	39(17)	8 (3)	3 (1)
Nausea	50(22)	2 (1)	0 (0)	36(15)	1 (0)	0 (0)
Constipation	44(19)	6 (3)	0 (0)	21(9)	2 (1)	0 (0)
Vomiting	42(18)	5 (2)	0 (0)	28(12)	2 (1)	0 (0)
Stomatitis	14 (6)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)
Mucosal inflammation	14 (6)	1 (0)	0 (0)	2 (1)	0 (0)	0 (0)
Metabolic/Nutritional						
Peripheral edema	24 (10)	2 (1)	0 (0)	13(6)	1 (0)	0 (0)
Hypomagnesemia (AE)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypomagnesemia (Lab)	87 (38)	6 (3)	2 (1)	5 (2)	0 (0)	0 (0)
Respiratory						
Cough	31 (14)	1 (0)	0 (0)	17 (7)	0 (0)	0 (0)
Skin/Appendages						
All skin/integument toxicity	210 (92)	42 (18)	1 (0)	46 (20)	4 (2)	1 (0)
Erythema	146 (64)	12 (5)	0 (0)	2 (1)	0 (0)	0 (0)
Acneiform Dermatitis	142 (62)	17 (7)	0 (0)	2 (1)	0 (0)	0 (0)
Pruritis	130 (57)	5 (2)	0 (0)	5 (2)	0 (0)	0 (0)
Skin exfoliation	56 (24)	5 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Paronychia	55 (24)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Rash	46 (20)	2 (1)	0 (0)	2 (1)	0 (0)	0 (0)
Skin fissures	45 (20)	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)
Dry skin	21 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other nail disorder	20 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

¹ Adverse reactions were coded using MedDRA dictionary V8.0. Version 2.0 of the NCI CTC was used for grading toxicities.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 4, 2006

TO: ~~Monica Hughes~~, Regulatory Project Manager, OND/OODP/DBOP
Ruthann Giusti, M.D., Medical Officer, OND/OODP/DBOP

THROUGH: Leslie Ball, M.D., Branch Chief, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

FROM: J. Lloyd Johnson, Pharm.D., Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations 

SUBJECT: Evaluation of Clinical Inspections

BLA: STN BL 125147/0

APPLICANT: Amgen, Inc.

DRUG: Panitumumab (rHuMAb-EGFr, Human Monoclonal Antibody to Human Epidermal Growth Factor Receptor)

CHEMICAL CLASSIFICATION: 1S (New Molecular Entity, Priority Review)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Metastatic Colorectal Cancer

CONSULTATION REQUEST DATE: March 10, 2006

GOAL DATE TO PROVIDE CLINICAL INSPECTION SUMMARY: August 15, 2006

ACTION GOAL DATE: September 8, 2006

I. BACKGROUND

Amgen Inc., submitted a Biologic License Application (BLA) for panitumumab, a monoclonal antibody cancer treatment agent classified as an epidermal growth factor inhibitor. Panitumumab is a fully human epidermal growth factor monoclonal antibody that targets epidermal growth factor receptors in tumor cells and blocks the binding of epidermal growth factor (EGF) and transforming growth factor (TGF) proteins reported to be responsible for stimulating tumor cell growth.

Based on study results, Amgen claims that panitumumab demonstrates antitumor activity in subjects with advanced refractory colorectal cancer. Amgen is seeking a treatment indication in subjects with Metastatic Colorectal Cancer.

Study 20020408 was the primary focus of the bioresearch monitoring clinical investigator inspections conducted for this BLA submission.

II. RESULTS (by site):

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECTN DATE	EIR-REC'VD	FIELD CLASS.
Alain Hendlisz, M.D. (Site 1102)	Brussels	Belgium	Study 20020408	May 8 – May 9, 2006	June 28, 2006	NAI
Yves Humblet (Site 1104)	Brussels	Belgium	Study 20020408	May 10 – May 12, 2006	June 28, 2006	NAI
Marc Peeters (Site 1103)	Gent	Belgium	Study 20020408	May 15 – 19 2006	June 30, 2006	NAI
Salvatore Siena (Site 1401)	Milano	Italy	Study 20020408	May 22 - 25, 2006	July 3, 2006	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

VAI= Deviation(s) form regulations, response requested. Data acceptable

OAI = Significant deviations from regulations. Data unreliable

Pending = Inspection/Report not completed

Study Protocol:

ABX-EGF 20020408: An open-Label, Randomized, Phase III, Clinical Trial of ABX-EGF plus Best Supportive Care vs. Best Supportive Care in Metastatic Colorectal Cancer.

The inspections audited Study Protocol 0020408. Study 20020408 is an open-label, randomized, multicenter Phase 3 study of ABX-EGF plus best supportive care (BSC) versus BSC in subjects with metastatic colorectal cancer. The study is designed to assess whether ABX-EGF plus BSC improves

progression-free survival time compared with BSC alone as third or fourth line therapy in subjects with metastatic colorectal cancer. Eligible subjects were randomized in a 1:1 ratio to receive ABX-EGF plus BSC or BSC alone as third or fourth-line treatment.

A total of 463 subjects, with 232 and 231 subjects per treatment group from 81 study sites in Europe, Canada, Australia and New Zealand (no U.S. sites) were enrolled in the study. Study subjects were administered ABX-EGF by IV infusion at a dose of 6 mg/kg once every 2 weeks for up to 48 weeks.

The Primary endpoints include: Progression Free Survival (date of randomization to date of adjudicated radiographic progression or death).

The Secondary endpoints include: overall survival, objective response, duration of response, and patient-reported outcomes.

Study subjects were assessed for safety by monitoring adverse events, changes in laboratory values and incidence of HAMA formation.

The subject accrual period is for 12 months, the treatment phase was for a maximum of 48 weeks. The study was initiated on January 16, 2004 and concluded on June 30, 2005.

The inspections audited a total of four foreign clinical investigators that participated in Study 20020408. The clinical investigator inspections were conducted under the Bioresearch Monitoring Program (CP 7348.811). The clinical investigator audits were issued by DSI in consultation with the BLA Review Committee.

Basis for site selection: The following sites were selected for inspection because of their high enrollment. Site selection was based on the number of subjects enrolled. The Division of Biologic Oncology Products (DBOP) selected the highest enrolling foreign sites for the inspections. DBOP did not identify any specific problems with the study data or specific areas to emphasize during the inspections.

- (1) Alain Hendlisz (Study 20020408) (Site 1102) (21 Subjects)
Institut Jules Bordet
Rue Heger Border 1
Brussels, Belgium 1000

Inspection dates: May 8 – 9, 2006.

Methodology: Inspection assignments were issued to the field office.

- a. What was inspected?
Records of 30 subjects pre-screened and 21 subjects randomized in the study were reviewed.
- b. Limitations of inspection: The clinic hospital records and all laboratory and radiology records were in French. A translator was required to read and review some portions of the records.
- c. General observations/commentary: Subject records were reviewed and compared with sponsor's data listings. In general, the case report forms (CRFs) were found to

be accurate and reflected the source documents on site. Study records were legible, well organized and contain adequate information. In general, Dr. Hendlisz adhered to protocol procedures. Protocol deviations were as reported by the firm.

No significant deviations were noted during the inspection. No FDA-483 was issued.

Recommendation: Data from this site are acceptable.

- (2) Yves Humblet (Study 20020408) (Site 1104) (23 Subjects)
Cliniques niversitaires Saint Luc
Avenue Hippocrate 10
Brussels, Belgium 1200

Inspection dates: May 10 – 12, 2006.

Methodology: Inspection assignments were issued to the field office.

- a. What was inspected?

The study records of 23 subjects enrolled in the study were audited.

- b. Limitations of inspection: The clinic hospital records and all laboratory and radiology records were in French. A translator was required to read and review some portions of the records.

- c. General observations/commentary: Audit of the site included review of informed consents, CT scans, subject records, study correspondence records, drug accountability records. In general, CRFs were found to accurately reflect source documents and the study was monitored by the sponsor on a regular basis. Adverse events were accurately reported. The PI and study staffs were found to be very cooperative and very receptive to comments throughout the inspection. Minor observations were discussed at the conclusion of the inspection.

No FDA-483 was issued.

Recommendation: Data from this site are acceptable.

- (3) Marc Peeters (Study 20020408) (Site 1103) (63 Subjects)
Universitair Ziekenhuis Gent
De Pintelaan 185
Gent, Belgium 9000

Inspection dates: May 15 – 19, 2006.

Methodology: Inspection assignments were issued to the field office.

- a. What was inspected?

The study records of 63 Subjects enrolled in the study were audited.

- b. Limitations of inspection: Limitations of inspection: The clinic hospital records and all laboratory and radiology records were in French. A translator was required to read and review some portions of the records.

- c. General observations/commentary: 90 subjects were screened and 63 subjects were enrolled

in the study. A comprehensive review of the records of four study subject records was conducted. The audit covered data listings, X-rays, spiral CTs, lab reports, histopathology reports, tissue blocks, drug administration sheets, and consent forms. In general the records were found to be in good order, the PI adhered to protocol requirements. No significant issues were found but several minor items related to the need for improvements in documentation practice were discussed at the conclusion of the inspection.

No FDA-483 was issued.

Recommendation: Data from this site are acceptable.

- (4) Salvatore Siena (Study 20020408) (Site 1401) (34 Subjects)
Ospedale Niguarda Ca Granda
Piazza Ospedale Maggiore 3
Milano, Italy

Inspection dates: May 22 – 25, 2006

Methodology: Inspection assignments were issued to the field office.

- a. What was inspected?
The study records of 34 subjects enrolled in the study were audited.
- b. Limitations of inspection: None
- c. General observations/commentary: 71 subjects were screened and 34 were randomized in the study. Several objectionable conditions/practices were noted during the inspection but most were resolved at the conclusion of the inspection. Dr. Siena was receptive to the suggestions and comments made at the conclusion of the inspection and stated that they will improve their operations for future studies.

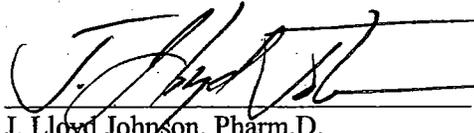
No FDA-483 was issued.

Recommendation: Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the four study sites inspected, it appears that sufficient documentation to assure that all study subjects audited did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

Follow-up action: none



J. Lloyd Johnson, Pharm.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments:



Leslie Ball, M.D.
Branch Chief, Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

DISTRIBUTION:

- HFD-47/Johnson
- HFD-45/Reading
- HFD-45/Program Management Staff (electronic copy)
- HFD-45/JR/JS
- File HFD-47/LB
- DBOP/MO (Ruthann Giusti, M.D.)
- DBOP/RPM (Monica Hughes)

Filename and path: O: BLA.STN.BL 125147/0.CIS.8.4.06



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 28, 2006

From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP

Subject: 125147/0: Standing Weekly Teleconference

FDA Attendees:

Monica Hughes
Ruthann Giusti

Amgen Attendees:

Julie Lepin
Mike Wolf
Jennifer Mercer
Allesandra Cesano
Sophie Visonneau
Mary Celine Scott
Barbara Mounho
Bing Bing Yang

Discussion: FDA asked Amgen if the 120 day safety update contained any of the PK data discussed during the July 14 and 21, 2006, teleconferences. Amgen confirmed yes, it can be found in the "all monotherapy" and "mCRC" datasets. Amgen confirmed they will be submitting the 6 mg/kg data for all 102 patients discussed during the July 21, 2006, teleconference shortly. FDA asked if this data would be broken down by the number of cycles received. Amgen confirmed yes.

FDA stated that we are currently working on revisions to the package insert. FDA wants to create an AE table that compares BSC to Panitumumab as the focus of the safety section. FDA agreed to work on this table and get back to Amgen with any questions.

**APPEARS THIS WAY
ON ORIGINAL**

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 2 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

Memorandum

Date: July 25, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: Labeling Meeting for 125147/0

Second team labeling meeting to discuss Amgen's proposed package insert for Vectibix™ which is indicated for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

FDA Attendees included:

Monica Hughes
Ruthann Giusti
Anne Pilaro
Angela Men
Hong Zhao
Patricia Keegan
Jennifer Rouine
Chana Fuchs
Kallapa Koti

Team agreed to continue making the remaining revisions via email prior to sending it to Amgen for comments.

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 21, 2006

From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP

Subject: 125147/0: Standing Weekly Teleconference

FDA Attendees:

Monica Hughes
Ruthann Giusti
Patricia Keegan
Angela Men
Hong Zhao
Chana Fuchs

Amgen Attendees:

Julie Lepin
Mike Wolf
Jennifer Mercer
Allesandra Cesano
Sophie Visonneau
Mary Celine Scott
Barbara Mounho
Bing Bing Yang

Amgen requested additional discussion at the teleconference this Friday, 21 July 2006, with regard to the following query and our proposed responses. Below is the information emailed from Amgen on 7/19/06.

Comparability: *Please clarify whether there is an ongoing study to determine the safety using the to-be-marketed formulation, — CHO. Or if you have additional data to support the comparability.*

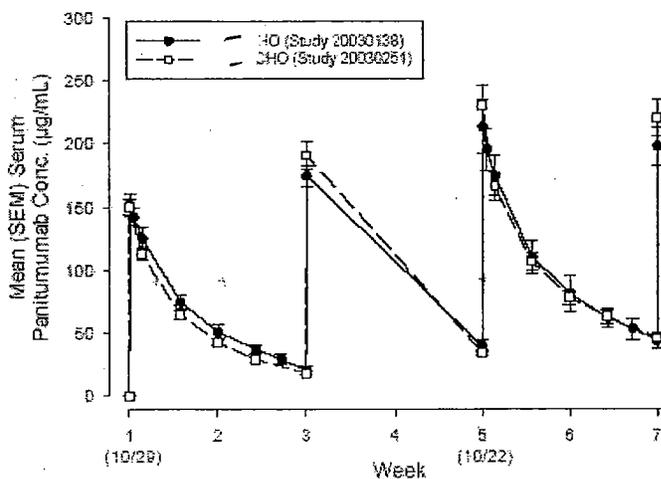
During our teleconference last week, Dr. Zhao noted that we did not establish bioequivalence of the — and — material and asked if we had additional data.

In order to support manufacturing changes incorporated during development, comprehensive comparability assessments were performed to evaluate the impact on changes to the quality and function of the molecule, and are reported in the BLA. The components of comparability involved complete biochemical and biophysical characterization, stability, nonclinical and clinical studies. Details of manufacturing changes incorporated during development and the supporting studies are described in Module 3, Section 3.2.S.2.6.1 (Manufacturing Process History). Pharmacokinetic comparisons for material produced by the different manufacturing processes are provided in Module 2, Section 2.7.2 (Summary of Clinical Pharmacology

Studies).

Specifically, as noted in Module 2.7.2.2.2, in study 20030251, the PK profiles of panitumumab were primarily evaluated to support the manufacturing change from a CHO process to a CHO process. The PK profiles after the first and third dose of 6 mg/kg Q2W were similar to those from Study 20030138, in which CHO-derived panitumumab was administered

Figure 8. Mean (SEM) Serum Concentration-time Profiles of Panitumumab at 6 mg/kg Q2W from a CHO Process (Study 20030138) and CHO Process (Study 20030251)



Numbers in parentheses below the x-axis are the number of subjects for the CHO/CHO cohorts, respectively, after the first and third doses.

Source: \\documentum\Docbases\usddms\R&D_Candidates\Development\AMG_954 - ABX-EGF\Preclinical Non-Study Specific\PKDMA\Submission\BLA\Clinical\Supporting_data\Graphs\138 and 251 vs comparison graph.JNB

Although these 2 studies were not designed and powered as bioequivalence studies, the 90% CIs of the parameter ratios were within or were slightly outside the 80 to 125% bioequivalence interval, indicating that the PK of panitumumab derived from the CHO and CHO processes were comparable.

APPEARS THIS WAY
ON ORIGINAL

Table 5. Summary of Statistical Evaluation of Panitumumab Pharmacokinetic Parameters at 6 mg/kg Q2W from a CHO Process (Study 20030138) and CHO Process (Study 20030251)

Parameter	CHO (test)			CHO (reference)			Ratio (test/reference)	90% CI
	Mean	%CV	n	Mean	%CV	n		
<u>After the first dose</u>								
AUC _{0-72h} (µg·day/mL)	744	26	29	862	21	10	85	71 to 101
C _{max} (µg/mL)	152	19	29	150	16	10	101	89 to 113
<u>After the third dose</u>								
AUC _{0-72h} (µg·day/mL)	1311	28	22	1306	29	10	99	83 to 120
C _{max} (µg/mL)	232	31	22	213	28	10	108	89 to 130

AUC_{0-72h} = area under the serum concentration-time curve during the dosing interval; C_{max} = maximum

observed concentration; mean = arithmetic mean; ratio = ratio of antilogs of treatment least squares

mean values expressed as a percentage; 90% CI = 90% confidence interval estimate for ratio

(test/reference) of treatment least-squares mean values expressed as a percentage

Source: Modified from Study Report 20030138 and Study Report 20030251.

Amgen would like to discuss potential additional analyses and what information they might provide. The pharmacokinetic analyses of the 9 mg/kg dose group is ongoing, and can be made available to the Agency to further characterize the profile of the material.

Dr Keegan asked what datasets would be included in the 120 day update, and specifically asked how much safety information with mCRC patients treated with material, dosed 6 mg/kg Q2W would be included. Dr. Keegan also asked if we could provide additional efficacy data from this formulation/regimen.

All tables and listings included in the CSS will be updated in the 120-day update. As requested, we will provide efficacy data from the two Phase 1 trials, 20030251 and 20040192 (in Japanese subjects) in which the scale panitumumab was used, in the 120 day update. A total of 24 subjects with metastatic colorectal cancer were included in these studies, 12 of whom were dosed with 6 mg/kg. Based upon investigator assessment, 6/24 of these subjects had partial responses.

All of the ongoing panitumumab trials are being conducted with material; at the current time, this includes ~ 550 subjects. A detailed description of these trials and the dosing regimens can be provided to the Agency if requested. Future trials in mCRC patients, including the confirmatory trial (20050181, second line) and a first line trial (20050203) will also use this material. As noted in the Risk Management Plan (Module 1.16), Amgen is committed to an ongoing post marketing safety surveillance program to ensure continued identification, assessment, communication, and management of risks associated with panitumumab treatment.

Discussion: FDA confirmed receipt of materials above emailed prior to this teleconference. Amgen asked if there are any areas related to comparability that they could address for us. FDA asked if Amgen could provide data using the 9 mg/kg dose. FDA asked what additional data Amgen could provide as supportive data in light of the bioequivalence data and lack of formal bioequivalence study in the to-be-marketed product.

Amgen stated that they can provide additional monotherapy data, including, data from 15 mCRC patients, 31 patients (→ 6 mg/kg) from a Japanese study, for a total of 65 from ongoing studies. FDA asked if Amgen had PK data in the Japanese population to ensure it is a comparable population. Amgen acknowledged they could provide this to FDA.

Based on the discussion, FDA stated that enough data may not be available to demonstrate comparability, and that data submitted could justify a major amendment. FDA would prefer to have data from 100 patients. Amgen stated that they may not be able to provide that until 2008. Amgen did state that they could take data from across different tumor types and put together a package for FDA review that would consist of 102 patients. FDA agreed to accept this data for review. However, Amgen needed to get back to FDA on a possible timeframe for submitting this information.

Amgen stated that per previous discussions, they cannot classify hepatic function patients per the guidance document as they used different criteria to characterize them. FDA asked Amgen to propose an alternative proposal. Amgen agreed to get back to us with their proposal.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 14, 2006

From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP

Subject: 125147/0: Standing Weekly Teleconference

FDA Attendees:

Monica Hughes
Ruthann Giusti
Patricia Keegan
Angela Men
Hong Zhao
Patrick Swann

Amgen Attendees:

Julie Lepin
Mike Wolf
Jennifer Mercer
Allesandra Cesano
Sophie Visonneau
Mary Celine Scott
Barbara Mounho
Bing Bing Yang

FDA requested to discuss the following at the 7/14/06 standing teleconference. These questions were forwarded to Amgen via email on 7/13/06.

1. Comparability: Please clarify whether there is an ongoing study to determine the safety using the to-be-marketed formulation, — CHO. Or if you have additional data to support the comparability.

Discussion During Teleconference: Amgen stated that the BLA contains data on 67 patients, this will be updated in the 120 day safety report to include 102 patients. Amgen noted that study 20050181 uses the — product and that all current studies have been amended and all use the — product. FDA expressed concern that Amgen had not established bioequivalence of the — and — material. FDA asked Amgen if any additional bioequivalence data was available.

FDA asked Amgen what was coming in the 120 day safety update besides AE reports. Amgen stated that they are submitting an updated integrated safety database, it will use the same tables originally submitted; however, they will be updated in tabular format.

FDA stated that it appears that the 120 day safety update will also contain new efficacy data.

2. In the PK and safety analysis, hepatic function was categorized as "impaired" (ALT or AST > 3 ULN or Bilirubin > 2 ULN) and "normal". Please clarify the criteria used to identify the mild, moderate and severe hepatic impairment in the "impaired" group, as well as the number of patients in each group in the Pop PK analysis.

Discussion During Teleconference: FDA asked if the Pop PK covariate will allow for breakdown of mild/moderate/severe hepatic impairment. Amgen stated that severe patients were excluded.

3. You state that race did not have impact on the PK of Panitumumab. In the Pop PK analysis, you compare the PK between the White (85%) and the Other (15%). Please clarify how you analyzed PK in the subgroup "Other", such as Asian, Black etc.

Discussion During Teleconference: FDA requested that race be broken out by groups. Amgen agreed to provide this information.

4. In the labeling, you claim that

Please

provide the datasets, which were used to create Figure 28 and 29 in Section 2.7.2.4.1 (Immunogenicity), Pages 68-69, as well as the matching efficacy and safety datasets, in SAS Transport formats.

Discussion During Teleconference: FDA asked if there is a variable in a dataset to see which patients formed antibodies. Amgen stated that this information is not in a dataset, PK was confirmed by visual inspection. Amgen could create a new dataset in mCRC patients with "+" and "-"s variables. Amgen will submit this information to the BLA.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 12, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: Labeling Meeting for 125147/0

First team labeling meeting to discuss Amgen's proposed package insert for Vectibix™ which is indicated for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

FDA Attendees included:

Monica Hughes
Ruthann Giusti
Anne Pilaro
Rajnikanth Madabushi
Angela Men
Hong Zhao
Patricia Keegan
Robert Becker
Nina Chace
Francis Kalush
Jennifer Rouine
Patricia Love
Max Robinowitz
Ruth Cordoba-Rodriguez
Chana Fuchs
Kallapa Koti

Team agreed to additional discussions were needed to get through the entire label prior to sending it to Amgen, RPM will change the August 16, 2006, meeting to a sooner date.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 7, 2006
From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP
Subject: 125147/0: Standing Weekly Teleconference

FDA Attendees:

Monica Hughes
Ruthann Giusti
Kaushikkumar Shastri
Patricia Keegan
Angela Men
Hong Zhao
Ruth Cordoba-Rodriguez
Chana Fuchs

Amgen Attendees:

Julie Lepin
Mike Wolf
Jennifer Mercer
Allesandra Cesano
Sophie Visonneau

FDA requested clarification regarding how patients were identified as "disease progression" by investigators but not progressed by the central review were handled in the PFS analysis. Do we have progression dates for central review for these patients and if so, how are they coded? Amgen stated there were a total of 33 of these discordant patients: 17 received BSC and 7 received panitumumab. Amgen confirmed patients remained in the treatment arm assigned.

FDA asked for patients censored by the central review committee, some were censored early, some late, some were lost to follow-up. Amgen stated that 25% did not cross over, some were deaths. Amgen would clarify for FDA in a submission to the BLA.

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2 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

Memorandum

Date: June 30, 2006
From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP
Subject: 125147/0: Standing Weekly Teleconference

FDA Attendees:

Monica Hughes
Ruthann Giusti
Kaushikkumar Shastri
Patricia Keegan
Angela Men
Hong Zhao
Ruth Cordoba-Rodriguez
Chana Fuchs

Amgen Attendees:

Julie Lepin
Mike Wolf
Jennifer Mercer
Allesandra Cesano

FDA requested an update regarding a request sent via email earlier in the week; Amgen stated this information would be submitted shortly.

The "control" and "result files" of NONMEM analysis for the **relevant** steps in model building and qualification (Sections 12.5.2 - 12.5.10 of the Population PK analysis report - Amgen PCSTD # 104311) do not appear to have been provided. If they have already been provided, please point out to the particular sections of the submission where they can be found. Otherwise, please submit the files in .txt format. Also provide a definition file which provides a brief description of the control files.

The data and the relevant SAS codes exploring the relationship between PK and Integument and eye toxicities (Exposure - Safety relationship) do not appear to have been submitted. If they have already been provided, please point out to the particular sections of the submission where they can be found. Otherwise, please submit.

FDA forwarded the following requests to Amgen via email shortly before the teleconference. Amgen agreed to provide the information requested below:

Statistical Questions:

1. Please explain why the Kaplan-Meier curve of overall survival for the BSC arm in the pre-BLA briefing package indicates a patient with a censored overall survival of 78 weeks, while the largest overall survival value in the submitted dataset for the BSC arm is a value censored at 70 weeks.
2. Please explain why the overall survival stratified log-rank test has a p-value given as 0.7033 in both the pre-BLA briefing package and the sponsor presentation, but the BLA submission indicates a respective p-value slightly larger than 0.6.
3. Please supply a derived dataset that has the actual number of prior lines of therapy for each patient.

CMC Questions:

4. The package insert mentions dilution in _____ We thought we heard in the quality section of the post submission briefing on 5/15/06) that Panitumumab should not be diluted in anything other than _____. Could you please tell us where that statement in the BLA for when we review the PI.
5. We noted that the animal data (pharm/tox) had Panitumumab diluted in buffer. Also, Please point us to the information in the BLA (or please submit additional information) – showing/supporting that dilution of Panitumumab in buffer will not impact distribution, toxicity, activity (in vivo) etc. in a different manner than in _____
6. Please provide drug substance and drug product release and stability tests results separately. In section 3.2.S.4.5 titled Justification of Specification _____ are summarized as pooled data from DS and DP. In addition, please identify which lots were considered in the result of the last column of the table 1 in the section mentioned above.
7. Please provide primary data for results of all peaks from the _____ test performed so far for all release, stability and reference standard product tested (CHO-derived).
8. Please provide primary data for results from the _____ test for all release, stability and reference standard CHO-derived lots tested.
9. Please provide primary data for all release and characterization tests performed for the CHO-derived reference standards used or in use.
10. Please clarify if any of the following drug product lots have been placed on stability and if so, please provide the data available for these lots. Lots: 954A047028, 954A047076, 954A041135, 954A043556.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 29, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: Mid-Cycle Review Meeting for 125147/0

The Mid-Cycle review meeting for this BLA was held on June 29, 2006, from 11:00 AM-2:30 PM.

FDA Attendees included:

Monica Hughes
Patricia Keegan
Ruthann Giusti
Kaushikkumar Shastri
Kallapa Koti
Mark Rothmann
Francis Kalush
Karen Weiss
Karen Jones
Anne Pilaro
Chana Fuchs
Martin Green
Melanie Hartsough
J. Lloyd Johnson
Steven Lemery
Ruth Cordoba
Patrick Swann
Karen Jones
Jennifer Rouine
Fatima Stimpson
Nam Rahman
Raj Madabushi
Yaning Wang
Brenda Uratani
Lydia Martyneec
Richard Pazdur
Janet Barletta

125147/0
Panitumumab (Vectibix®)
Amgen, Incorporated
Mid-Cycle Meeting Agenda
June 29, 2006 (11:00 AM-2:30 PM)

This is a new BLA, being reviewed under the CMA Pilot 1 program, with a 6-month priority review clock.

Proposed Indication:

Agenda:

1.	Review of Milestones by Monica Hughes	5 Minutes
2.	CMC Review: Presentation by Chana Fuchs	20 Minutes
3.	Facility Review: Presentation by Janet Barletta and Michelle Clark-Stuart	10 Minutes
4.	Pre-Clinical Review: Presentation by Anne Pilaro	20 Minutes
5.	Clinical Review and Statistical Review: Presentations by: Ruthann Giusti and Kallapa Koti	45 Minutes-1.5 Hours
6.	Clinical Pharmacology Review: Presentation by Angela Men	20 Minutes
7.	Discuss Labeling: Major Issues	
8.	Discuss upcoming Meetings: Labeling, ODAC and ODS Safety Conference	10 Minutes
9.	Discuss Path Forward	

Milestones:

First Committee Meeting: Held: April 27, 2006

Filing Meeting: Held: May 10, 2006

Filing Action Letter: Filed: May 24, 2006

Deficiencies Identified Letter: June 9, 2006

Discipline Review Letter Pre-Clinical: Issued on June 15, 2006

Discipline Review Letter CMC: *Due on August 29, 2006*

Mid-cycle Meeting: June 29, 2006

Labeling Meetings as Currently Scheduled:

#1: July 12, 2006: 11:00 AM-3:00 PM

#2: August 16, 2006: 12:00 AM-3:00 PM

#3: September 12, 2006: 11:00 AM-3:00 PM

* Note this time will also cover the ODAC Debrief and the ODS Safety Conference

ODAC: Tentatively scheduled for September 6, 2006

Final Action Due: *September 28, 2006*

Milestones were discussed and presentations were given by all team members regarding their reviews to date.

At the conclusion of the presentations, the review team and OODP management decided not to take this application to ODAC. The project manager was instructed to inform the company of the decision.

The meeting adjourned.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 8382

Amgen, Incorporated
Attention: Mary Celine-Scott, Ph.D., M.B.A.
Senior Manager, Regulatory Affairs
Amgen, Incorporated
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Scott:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Panitumumab Human Monoclonal Antibody (ABX-EGF) (Abgenix) to Epidermal Growth Factor Receptor

We have reviewed your February 1 and 15, 2006, submissions regarding your proprietary name for Panitumumab in consultation with CDER's Office of Drug Safety and the Division of Drug Marketing, Advertising, and Communication's, and have concluded that the proprietary name "Vectibix" is acceptable at this time under 21 CFR Part 201. Please note, this is considered a tentative decision. This name, along with its associated labels and labeling, must be re-evaluated approximately 90 days prior to the expected approval of the BLA. A re-review of the name prior to BLA approval will rule out any objections based upon approvals of other proprietary or established names subsequent to the signature date of this letter.

In the review of the proposed Vectibix labeling, we attempted to focus on safety issues relating to possible medication errors. We have identified the following areas of possible improvement, which might minimize potential user error.

GENERAL COMMENTS:

1. The concentrations expressed on the container labels and carton labeling are inconsistent with what is expressed in the insert labeling. In the insert labeling, all three strengths are stated to have a concentration of 20 mg/mL. However, in the container labels and carton labeling, the concentration varies from _____
Revise the labels and labeling to accurately reflect the actual contents of each vial.
2. The strength is expressed in terms of total 'mg per vial' without reference to a corresponding milliliter amount. Post-marketing evidence has demonstrated that omitting this information may lead to calculation errors. Thus, we request that you revise the expression of strength to include the total milligrams and milliliter. For example:

400 mg/20 mL
(20 mg/mL)
3. Since each vial is a single use vial, include a statement that indicates that the unused portion should be discarded. Otherwise, unused portions may be retained for future doses.
4. Ensure that the established name is as prominent as the proprietary name per 21 CFR 610.62 (b).

5. The strength is displayed more than once in its current presentation. Revise the labels and labeling so that the strength is prominently displayed only once.

CONTAINER LABEL:

6. See GENERAL COMMENTS.
7. The — color contrasted with the — (200 mg/vial) background color is difficult to read (see below in B-3). Revise the background color to improve readability of the strength, unit designations, and NDC number or use a darker font color so that it is contrasted with the color used for the numbers and letters. Also, please ensure that the new colors can be clearly differentiated from the 100 mg/vial and 400 mg/vial strengths.
8. The colors use to designate the 200 mg/vial and 400 mg/vial appear to be similar to one another when compared side-by-side. We believe that the similar colors have the potential to cause selection errors as the strength may be confused. We recommend revising the colors so that they are clearly differentiated from one another and from the 100 mg/vial strength.
9. The carton/package labeling should note the preservative used and its concentration; if no preservative is used and the absence of a preservative is a safety factor, then the words "no preservative" should be noted.
10. Please note that when the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit visual inspection of the contents (21 CFR 610.60).

CARTON LABELING:

11. See GENERAL COMMENTS and comments 7 and 8.
12. A ' — is present which interferes with the readability of the name. Reduce the prominence of — or remove it from the labeling.

INSERT LABELING:

13. See comment # 1.

We request that you resubmit all revised labels and labeling to BL STN 125147/0 at least 90 days ahead of the anticipated approval of the BLA. Please note, these are preliminary comments and additional comments may follow a comprehensive review of all Panitumumab labeling.

**APPEARS THIS WAY
ON ORIGINAL**

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, contact Monica Hughes, Regulatory Project Manager, at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED: 07/06/2006
DATE OF DOCUMENT: 06/27/2006

DESIRED COMPLETION DATE:
08/25/2006
PDUFA DATE: 09/28/2006

OSE REVIEW #:
05-0033-2

TO: Patricia Keegan, M.D.
Director, Division of Biological Oncology Products
HFD-107

THROUGH: Alina R. Mahmud, R.Ph., MS, Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Jinhee L. Jahng, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:
Vectibix
(Panitumumab)
100 mg/5 mL, 200 mg/10 mL, 400 mg/20 mL

SPONSOR: Amgen, Incorporated

BLA #: 125147/0 (IND 8382)

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Vectibix. We consider this a final review. However, if the approval of the BLA is delayed beyond 90 days from the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before the BLA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.
2. DMETS recommends implementation of the label and labeling recommendations outlined in Section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Vectibix acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND PACKAGING REVIEW

DATE OF REVIEW: August 16, 2006
BLA#: 125147/0 (IND 8382)
NAME OF DRUG: Vectibix (Panitumumab)
100 mg/5 mL, 200 mg/10 mL, 400 mg/20 mL
BLA HOLDER: Amgen, Incorporated

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Biological Oncology Products (HFD-107), for re-assessment of the proprietary name, "Vectibix", regarding potential name confusion with other proprietary or established drug names. Revised container labels, carton and insert labeling were provided for review and comment. The original labels and labeling were reviewed on February 6, 2006 in ODS Consult #05-0033-1.

PRODUCT INFORMATION

Vectibix (Panitumumab) is a recombinant human IgG2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Vectibix is indicated for

progression free survival. Currently no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Vectibix. The recommended dose is 6 mg/kg administered via an intravenous infusion pump once every 2 weeks

Vectibix will be available as an intravenous solution in single use vials containing 100 mg/5 mL, 200 mg/10 mL, and 400 mg/20 mL.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Vectibix to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Vectibix. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Vectibix acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Vectibix. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose	Other*
Vedtribx	Peritumumab 100 mg/3 mL, 200 mg/10 mL 400 mg/20 mL	6 mg/kg intravenous once every two weeks	
Fertinex (Discontinued)	Urofollitropin Injectable 75 IU/AMP, 150 IU/AMP	Assisted reproductive technology – <u>Female infertility – Test tube ovum fertilization</u> - Administer 150 international units intramuscularly or subcutaneously daily until follicular development, usually within 10 days; therapy should be initiated early in the follicular phase (menstrual cycle day 2 or 3) <u>Polycystic ovary syndrome, Not first-line therapy, for use after failure of clomiphene</u> – a) initial 75 international units intramuscularly daily for 7-12 days (usually followed in 1 day by human chorionic gonadotropin 5000 – 10,000 international units); in cases of inadequate follicle development, urofollitropin may be continued beyond 12 days; following 2 courses of urofollitropin in which ovulation but not pregnancy occurs, dose may be increased to 150 international units. b) initial 75 international units subcutaneously daily; adjust dose after 5-7 days by no more than 75 international units/day depending on patient response; dose range 75-300 international units/day (usually followed in 1 day by human chorionic gonadotropin 5000 – 10,000 international units); urofollitropin dose for subsequent cycles should be based on response in the preceding cycle.	LA
Ventolin HFA	Albuterol Sulfate Aerosol 90 mcg/actuation	Two inhalations by mouth every 4 to 6 hours.	S/LA
			LA
Vistide	Cidofovir Injection 75 mg/mL	Induction therapy: 5 mg/kg intravenous once a week for 2 consecutive weeks; give probenecid and saline pre-hydration with each infusion. Maintenance therapy: 5 mg/kg intravenous once every 2 weeks; give probenecid and saline pre-hydration with each infusion.	LA
<p>*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) ***Name pending approval. Not FOI releasable.</p>			

B. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Vectibix, the primary concerns relating to look-alike and sound-alike confusion with Vectibix are Fertinex, Ventolin, —, and Vistide.

1. Fertinex and Vectibix resemble each other in appearance when scripted. Fertinex is a discontinued drug product containing urofollitropin and is indicated for the stimulation of follicular recruitment and development and the induction of ovulation in patients with polycystic ovary syndrome and infertility, who have failed to respond or conceive following adequate clomiphene citrate therapy. It may also be used to stimulate the development of multiple follicles in ovulatory patients undergoing Assisted Reproductive Technologies (ART) such as in vitro fertilization. According to the 2004-2005 Annual Report, Fertinex was delisted on June 18, 2003 and is no longer distributed in the United States.

The first four letters, "Fer-" and "Vec-" resemble each other when scripted, especially if loop in "F" is not closed completely (see sample below). The middle letters "-ti-" are identical and each name has eight letters each. If the "b" is not scripted prominently, the "-bix" may resemble the "-nex" in Fertinex. However, DMETS believes the actual possibility for confusion with Vectibix to be minimal given Fertinex is no longer distributed in the United States and that it targets a narrow population of patients.

2. Ventolin HFA was found to have look-alike similarities with Vectibix, if the modifier, "HFA", is omitted. The omission of modifiers is a common source of error⁷. Research supporting the omission of modifiers was published in the Journal of Internal Medicine by Timothy S. Lesar. Thus, we must evaluate potential look-alike similarity without the modifier. Ventolin HFA is a sympathomimetic bronchodilator containing albuterol sulfate. Ventolin HFA is indicated for the relief and prevention of bronchospasm in patients with reversible obstructive airway disease and prevention of exercise-induced bronchospasm. The recommended dose is usually 2 inhalations every 4 to 6 hours. Each actuation delivers 90 mcg.

Ventolin HFA and Vectibix have similar looking beginnings ("Vent-" vs. "Vect-") and endings ("-lin" vs. "-bix"). Additionally, they both have eight letters and have upstroke characters ("t" and "l") which fall in the same order of each name (fourth and sixth position). However, Ventolin HFA and Vectibix vary with respect to dosage form (aerosol vs. injection), route of administration (oral vs. intravenous), frequency of administration (4 to 6 times daily vs. once every two weeks —), and dosage strength (90 mcg per actuation vs. 100 mg/5 mL, 200 mg/10 mL, and 400 mg/20 mL). Despite some similarities in appearance, DMETS believes the potential for confusion is minimized because of their product differences.

* Name pending approval. Not FOI releasable.

Lesar, Timothy S. Prescribing Errors Involving Medication Dosage Forms. *Journal of General Internal Medicine* 2002; 17:579-87.

refrigerated. Although they share some look-alike and product characteristics, DMETS believes the potential for confusion to be minimized given their different storage conditions and prescriber and patient populations.

*misbide
vectibix*

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Vectibix, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement, which might minimize potential user error.

A. CONTAINER LABELING

No comments.

B. CARTON LABEL

No comments

C. INSERT LABELING

1. In the "Dosage and Administration" section, include the route of administration in the directions, immediately following the dose.
2. The infusion rate is embedded in the "Preparation and Administration" section. We note that this drug should not be administered as an intravenous push or bolus. Therefore, we also recommend including this information in the "Dosage and Administration" section as this information pertains to the administration of the drug.



Our STN: BL 125147/0

Amgen, Incorporated
Attention: Alessandra Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

JUN 15 2006

Dear Dr. Cesano:

We have reviewed the PRE-CLINICAL section of your biologics license application (BLA) for Panitumumab. Here is a summary of preliminary comments, deficiencies, and questions identified during this review:

1. We note from our review of the pharmacology and toxicology data submitted to STN BL 125147/0 that the reported affinity for the hybridoma-derived Panitumumab appears to be approximately 10-fold less than that of the CHO-derived material. Study #R2005552, which evaluated the affinity of hybridoma-derived, ABX-EGF was conducted in 1996, while Study #R2005582, with the CHO-derived material produced at commercial scale was conducted in October of 2005. While no remarkable differences in either tissue cross-reactivity or toxicity were noted between products manufactured by the two methods (Studies #102920 and #103917, respectively), we note that some of the early pharmacology studies in human tumor xenograft models showed marked differences in the responsiveness of the same tumor lines to different preparations of Panitumumab, particularly in those xenograft models only partially responsive to Panitumumab, e.g., SK-MES lung or MiaPaCa pancreatic tumor lines (please see Comment #4, below).

Please address the impact of the apparent differences in affinity of Panitumumab produced by the two different manufacturing processes for EGFr, in the context of the overall nonclinical pharmacology and toxicology development program, and specifically regarding the anti-tumor efficacy of ABX-EGF in human tumors.

2. The final report for Study #R2005552 describes the binding affinity of the native ligand EGF for the EGFr as 3×10^{-9} M, or approximately 60-fold less than that of Panitumumab. However, the data in the literature article cited in the final study report show that the K_D for native EGF to EGFr is 7×10^{-9} M, 5×10^{-9} M, or 3×10^{-9} M on A431 human epidermoid carcinoma cells, and the 29R2 and 4 EGFr variant clones of A431 human tumor cells, respectively (Gill *et al.*, *J. Biol. Chem.*, 259:7755-7760, 1994). It is not clear from the information cited in the final report for Study #R2005552 whether the stated affinity constant of EGF for the EGFr was measured using the same conditions as the present study *i.e.* the BIAcore assay, or whether it was measured in the cellular assay, and

which cell line was described. Please clarify how the affinity of EGF for the EGFr on the three different cell lines was obtained, which cell line was described for the comparison of native EGF and ABX-EGF binding to the EGFr, and how any differences in the methodology used may modify statements that Panitumumab binding affinity to EGFr is approximately 60-fold greater than native EGF.

3. The final study report for Study #R2003094 does not indicate which antibody (ABX-EGF or M225) was used to generate the quantitative data on receptor number for each of the different cell types by flow cytometry. It is feasible that the two antibodies may bind EGFr with different affinities, and may not accurately reflect the actual receptor number present on the tumor cell lines. Please provide this information, and discuss how any differences in affinity between the two anti-EGFr antibodies may impact the apparent anti-tumor activity of ABX-EGF, as compared to published results for the same tumor cell xenograft models using the 225 antibody.
4. We note from our review that Study #R2003094 demonstrated relatively high numbers of EGF receptors on the surface of all five of the tested human lung and pancreatic tumor cell lines, as measured by flow cytometry. Additionally, Study #R2005548 showed relatively high cell surface EGFr staining with the commercial, EGFr pharmDx diagnostic kit on both the Panc-1 and MiaPaCa tumor samples (3⁺ intensity for both). However, in Study #R2003110, no effects of ABX-EGF antibody treatment at concentrations ranging from 0.03 nM to 3300 nM were observed in *in vitro* cellular cytotoxicity assays using the EGFr-positive, human H1299 and MV522 lung carcinoma, and Panc-1 and MiaPaCa pancreatic tumor cell lines, which were highly EGFr positive by flow cytometry. Additionally, the anti-proliferative effect of ABX-EGF was much weaker than anticipated in the SK-MES line, which demonstrated high levels of receptor binding (approximately 98,000 EGF receptors/cell) in Study #R2003094. Please comment on the apparent lack of any *in vitro* anti-proliferative effects of ABX-EGF on four of the five tested cell lines including Panc-1, which had the highest level of EGFr expression in Study #R2003094.
5. Based on the data presented in Study #R2005548, there does not appear to be any correlation between the level of EGFr expression detected on the cell surface by the EGFr pharmDx kit, and the apparent responsiveness of the tumor to Panitumumab treatment in xenograft models in nude mice. For example, both HT-29 and Colo 205 were found to express EGFr at a 2⁺ level in this study, but Colo 205 was not responsive to ABX-EGF treatment *in vivo* (Study #R2003325), while the HT-29 tumor did respond (Study #R2003327). We also note in our review that U87-MG vIII cells genetically modified to express a truncated form of the EGFr failed to respond to ABX-EGF treatment in murine xenograft models (Study #R2003550), even though in *in vitro* treatment of cultured, EGFr expressing U87-vIII cells Panitumumab inhibited the phosphorylation of EGFr-associated p1068 kinase, and completely down-regulated EGFr cell surface expression (Study #R2004440), and cell surface staining using the EGFr pharmDx commercial diagnostic kit was positive (3⁺ intensity; Study #R2005548) for this cell line.

Taken together, these data and those cited in Comment #4, above would appear to cast doubt on your present hypothesis that the cytotoxic effects of ABX-EGF are related to the expression of EGFr on the target tumor cells. Please comment on the apparent lack of correlation between cell surface EGFr expression and anti-tumor response to Panitumumab.

6. The results for Secondary Pharmacology Studies #R20045181 and #R2005428 appear to be identical, even to the percent inhibition of tumor growth observed in the Panitumumab monotherapy and combination dose groups. It is unclear from the way the study reports are written as to whether these effects are accurate, or if the report was inadvertently duplicated. Please clarify.
7. The final report for Pharmacokinetics Study #104275 states that the electrochemiluminescence (ECL) assay used had been validated using monkey serum as the matrix; however, this assay was performed in mice, and there was no information in the BLA submission as to whether the ECL assay had been validated, or even qualified with mouse serum as the matrix. Differences in binding proteins (*i.e.* albumin), and potential inhibitory or other factors in mouse serum may interfere with this assay, and result in changes in the expected serum concentrations of Panitumumab. Please provide information that addresses these issues, *i.e.* demonstrates a lack of effect of the mouse serum matrix as compared to the monkey serum.
8. The tissue samples in the *in vivo* tissue cross-reactivity study of ABX-EGF (Study #ABG09) were presumably obtained from one or more of the completed, GLP toxicity studies of Panitumumab in cynomolgus macaques. The Discussion section of the final study report states that the immunohistochemistry portion of the study was “blinded” such that the personnel at the contracting laboratory were unaware of the animal treatment conditions. However, there was no information provided in the final study report regarding the source (*i.e.* study number) from which these samples were derived, and as such, it is very difficult to determine the exposure to ABX-EGF that these animals achieved, and correlate that with both the tissue distribution patterns observed in the present study, and the previous toxicology results. Please provide the source [*i.e.*, Toxicology Study Number(s)] of the tissues evaluated for this study.
9. The sinusoidal staining observed in the livers of 5/10 monkeys in Group 4 from the *in vivo* tissue cross-reactivity study of ABX-EGF (Study #ABG09) may be related to Fc receptor-mediated clearance of ABX-EGF by Kupffer cells and other sinusoidal lining cells. We note from our review that no staining of these cell types was reported for liver sections from the other three dose groups, suggesting that Group 4 received the highest, *in vivo* exposure to ABX-EGF, and that saturation of EGFr was achieved at that dose, leaving more Panitumumab available for non-specific interaction with Fc receptors. However, no data were provided in the BLA submission that address whether Panitumumab can bind to monkey Fc receptor. Please comment.
10. Recommendations for revisions to the WARNINGS and PRECAUTIONS section of the proposed package insert will be communicated to you in the future as part of the labeling

discussions for the Clinical Reviewable Unit, and as agreed to under FDA's Continuous Marketing Application pilot 1 program.

We are providing these comments before completing our review of your entire application to give you advance notice of PRE-CLINICAL issues that we have identified. These comments are subject to change as we complete the review of your application. You may, but are not required to, respond to these comments. If you respond, we may or may not consider your response before taking a complete action on your application. If we determine that your response constitutes a major amendment, we will notify you of this decision in writing. We are continuing to review the remaining sections of your application. We will send you final comments, to which you must respond, after completing our review.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, M.S., at (301) 796-2320.

Sincerely,



Martin Green, Ph.D.
Team Leader
Division of Biological Oncology Products
Office of Drug Oncology Products
Center for Drug Evaluation and Research

RPM - Communication Screen Data Check

Letter Type: Discipline Review Letter (DR)

Summary Text: [Identify Discipline - Pick One]: Pharm Tox
Pre-clinical

cc: Monica Hughes
Karen Jones
Anne Pilaro
Martin Green
Patricia Keegan
Karen Weiss
Richard Pazdur
DBOP Division file (hard copy)

History: Hughes\6-14-06\

File Name: N:\DBOP\hughesm\Panitumumab\125147\0\Discipline Review Letter 125147\0
preclinical.doc

Division	Name/Signature	Date
OODP/DBOP	Monica Hughes	6-15-06
OODP/DBOP	Karen D. Jones	6-15-06
OODP/DBOP	Martin D. Green	6-15-06
OODP/DBOP	Kelly A. Pauroano	6/16/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125147/0

JUN 09 2006

Amgen, Incorporated
Attention: Alessandra Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Cesano:

Please refer to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, and to our filing letter dated May 24, 2006. While conducting our filing review we identified the following potential review issues as discussed during the June 9, 2006, teleconference between representatives of Amgen and FDA:

1. The following comments refer to Table 9-12 "Baseline Membrane EGFR Staining Intensity for Responders and Non-Responders throughout the Study (Central Assessment)".

In BL STN 125147/0, clinical study report 20020408, Table 9-12 (p. 184), responders (N=19) are compared with non-responders (N=212) by EGFR status in the Panitumumab + BSC arm. This comparison was not made in the BSC alone arm because nobody responded in that arm. From Table 9-12, the mean % cells with positive staining was 41.1% for responders and 33.5% for non-responders. Our t-test analysis indicates a non-significant difference ($p = 0.29$), but nonetheless suggests that response rate increases with increasing % stain. Similar non-significant but suggestive results obtain for % cells with membrane staining. Receiver operating characteristic (ROC) curve analysis is preferred to the t-test because fewer assumptions are made with it and it could provide extra power to detect that EGFR expression is informative for response. For the clinical endpoint of best objective response, Panitumumab + BSC arm, please construct ROC curves for each of the four EGFR measurements: % cells with positive staining, % cells with membrane staining, maximum EGFR staining intensity, and % cells with cytoplasmic staining. For each ROC curve, please test if the area under the curve (AUC) is greater than that expected by chance (0.5).

The results given in Table 9-12 are on the All Enrolled Analysis Set. A similar table was not included for the Adjudicated Prior Failures Analysis Set, which although is not an intention to treat (ITT) dataset, could reveal a significant association between EGFR expression and response status for the intended use population. Therefore, for the Adjudicated Prior Failures Analysis Set, please also perform the same ROC analyses as indicated above.

Amgen agreed to provide these data analyses to 125147/0.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, M.S., at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

CONCURRENCE PAGE

RPM - Communication Screen Data Check

Letter Type: Deficiencies Identified (DI)

Summary Text: Filing Issues Letter

RPM – Milestone Screen Data Check

Confirm “Deficiencies Identified” Entry and Close Date

cc: Division BLA Files
Monica Hughes
Patricia Keegan
Ruthann Giusti
Kaushikkumar Shastri
Anne Pilaro
Chana Fuchs
Ruth Cordoba-Rodriguez

History: Hughesm\6-6-06\6-9-06: K. Townsend: 6.9.2006

File Name: N:\DBOP\hughesm\Panitumumab\125147\0\Deficiencies Identified Letter 125147\0.doc

Division	Name/Signature	Date
00DP DBOP	Karen D. Jones for Dr. Hughes	6/9/06
DBOP	Karen D. Jones	6/9/06
DBOP	P. Keegan	6-9-2006
DBOP	K. Townsend	6-9-06

Date, 5/24/2006

Time 6:30 pm

FDA participants: Chana Fuchs

J 5/18/06

Amgen participants: Jennifer Mercer

Telephone no: 805-447-1285

Telecon notes:

In preparation for the PAIs, I called to find out where data is located.

Stability – primary and commercial — is located in — Supporting — is located at Immunex/Amgen in Washington.

Release testing – depends on methods, so some will be at Fremont, some at —

In process testing data for DS is at freemont

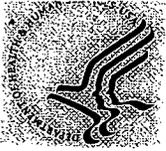
Comparability depends on test. A lot of it is at Immunex, Washington.

She will e-mail me an updated list of methods and locations.

They will be able to get data from Washington when we are there.

Follow-up e-mails were received from Jennifer Mercer with the information.

**APPEARS THIS WAY
ON ORIGINAL**



OUR STN: BL 125147/0

Amgen, Incorporated
Attention: Allesandra Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

MAY 24 2006

Dear Dr. Cesano:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated March 28, 2006, for Panitumumab to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The review goal date is September 28, 2006. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before June 11, 2006.

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, at (301) 796-2320.

Sincerely yours,

Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Concurrence Page

Application Number: BLA 125147/0
Letter Type: Filing Notification (FL)

cc: Division BLA Files
Monica Hughes
Patricia Keegan
Ruthann Giusti
Kaushikkumar Shastri
Anne Pilaro
Chana Fuchs
Ruth Cordoba-Rodriguez

History: Hughesm\5-23-06\

File Name: N:\\DBOP\hughesm\Panitumumab\125147\0\Filing letter 125147\0

Concurrence box

Office	Name/Signature	Date
DBOP/OOSP	Mon Hughes	5-23-06
OOSP/DBOP	Karen D Jones	5-24-06
DBOP	P. Keegan	5-24-06
OOSP/DBOP	Kelly Paumona	5/26/06

Date May 22, 2006

Time 4:05 pm

FDA participants: Chana Fuchs

Amgen participants: Jennifer Mercer

Telephone no: 805-447-1285

Telecon notes:

J 5/18/06

Jennifer Mercer called to get fedex address for a desk copy of the DMF and also will be submitting the qual data for characterization assays.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 15, 2006
From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP
Subject: 125147/0: Amgen's Post-Submission Briefing

Attendees:
See attached list.

Discussion: See attached slide-deck presented by Amgen.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MEETING ATTENDANCE LIST

Meeting between Amgen, Inc. and
the Center for Drug Evaluation and Research.

DATE: May 15, 2006 TIME: 2:00 -3:00 AM ROOM: WO, 1311 & 1313

NAME - Please print	AFFILIATION
Monica Hughes	Reg. Project Manager DBOP/CDER
ALESSANDRA CESANO	Clinical - AMGEN Inc.
Mary Celine Scott	Regulatory - Amgen
Judy Vong	Regulatory - Amgen
Michael Wolf	Biostatistics - Amgen
Barbara Mounho	Toxicology - Amgen
LEO SNEL	OPERATIONS - AMGEN
Michael Mulkearn	Analytical - Amgen
At Michael Mullenix	Clinical Immunology Amgen
BING - BING YANG	Pharmacokinetics Amgen
Jennifer Mercer	Amgen - Regulatory Affairs CMC
Robert Radinsky	oncology research - Amgen
RAFAEL AMADO	Clinical Development - Amgen
JULIE LEPIN	Regulatory Affairs - Amgen
SOPHIE VISONNEAU	Clinical - Amgen
Kallappa Kati	Statistician FDA
Anne Polaro	pharm/tox, FDA
Clara Fuchs	DMA - FDA
Angela Yuzin Men	Clinical Pharm - FDA
HONG ZHAO	clinical pharmacology - FDA
Patricia Keegan	CDER/OND/OODP/DBOP
Ruthy Gant	" " "
Michelle Y. Clark - Stuart	FDA/CDER/CMC
Raj Madabushi	PDA/CDER/OCP/PA
Michael Orr	FOA/CDER/OCP/Genomics
Ed Rock	DDOP/OODP/CDER
Joga Gobburu	FDA, pharmacometrics
V. LLOYD JOHNSON	FDA/PSI
Scott Kopsitz	FDA/Visiting Fellow
Ruth Cordoba-Rodriguez	FDA/DMA
FRANCIS KALUSH	FDA/OIVD/CDRH
Gene Pennello	FDA/OSB/CDRH
Mark Rothmann	FDA/CDER/OB
R PAZDUR	FDA

H

246 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

Memorandum

Date: May 10, 2006
From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP
Subject: 125147/0: Filing Meeting

Attendees:

Monica Hughes
Karen Jones
Patricia Keegan
Martin Green
Hong Zhao
Angela Men
Ruthann Giusti
Kallapa Koti
Anne Pilaro
Kaushikkumar Shastri
Chana Fuchs
Ruth Cordoba-Rodriguez
Patrick Swann
Jennifer Roiune
Susan Lu
Lloyd Johnson
Janet Barletta
Michelle Clark-Stuart
Patricia Love
Nina Chace
Maria Chan

Milestones: The filing letter must issue by May 28, 2006, and the deficiencies Identified letter must issue by June 11, 2006.

Discussion: The majority of the discussions involving the filing decision occurred during the February 2, 2006, acceptance meeting for the first reviewable unit received, the preclinical unit and the March 29, 2006, acceptance meeting for the second reviewable unit received, the CMC/quality unit.

The PREA form has been completed.

Discussion also involved the possibility of this application going to ODAC and discussions for to determine the necessity of taking this application to ODAC will continue during the review cycle.

There were no major issues with missing data in the clinical reviewable unit discovered at this time and this BLA is accepted for filing.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Panitumumab BLA telecons

Date May 8, 2006

Time 5:00 pm

FDA participants: Chana Fuchs

Amgen participants: Jennifer Mercer

Telephone no: 805-447-1285

Telecon notes:

I called Amgen requesting help in finding the following information in the BLA document for filing review purposes:

1. where to they state that the consistency/validation lots of DS and DP are manufactured consecutively?
2. comparability information in the BLA now contains murine hybridoma / — , to CHO (Amgen) studies. Where are
 - a. CHO (Amgen) to CHO (Abgenix) comparability report
 - b. Drug product — to — comparability report
3. where can I find validation/qualification for the additional characterization assays (ones used for comparability, setting up the reference standards, etc). Jenifer did not think they are included, and did not think these assays are fully validated like the lot release assays. I told her qualification reports would be good enough.
4. for DP batch records, some are comprehensive in that they cover all three sizes. However, the — batch record is only for 5cc vials. Did they also include somewhere the 10 and 20 cc vials?)
5. form 356h should indicate whether the facilities described are ready for inspection. I cannot find that statement. Please let me know where its located. I believe Monica Hughs may have already asked this, but I'm repeating since I have her on the phone.

Jen will look into this and let me know.

6:15 – Jen Mercer called back with the following:

1. consecutive is in the QOS section 2.3.S.2.2.5 (“the results of the process validation studies performed on 4 consecutive lots demonstrate...”) **She still has to get back to us re consecutive DP lots**
2. comparability is contained in an attached report to section 3.2.S.2.6 — in 6.1.8 2 reports referenced – attached. The complete comparability report is provided in Section 3.2.S.2.6.1.11 (Comparability Reports).
 - b. DP – not report, but a brief summary – in DP 3.2.P.3.5
3. **qualification data for additional characterization is not in here but will be submitted.**
4. **batch record – she will check for an executed batch record for DP in other vial sized for this step. I was not sure if the machine or process is identical or not.**
5. **ready for inspection was not submitted – an oversight will update the BLA.**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 28, 2006

From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP

Subject: 125147/0: First Committee Meeting

Attendees:

Monica Hughes

Karen Jones

Patricia Keegan

Martin Green

Hong Zhao

Angela Men

Ruthann Giusti

Kallapa Koti

Anne Pilaro

Kaushikkumar Shastri

Chana Fuchs

Ruth Cordoba-Rodriguez

Patrick Swann

Jennifer Roiune

Susan Lu

Lloyd Johnson

Janet Barletta

Michelle Clark-Stuart

Patricia Love

Nina Chace

Maria Chan

STN BLA 125147/0
Panitumumab (Trade Name Under Review)
First Committee Meeting Agenda
4/27/06

Review Team:

Monica Hughes, Regulatory Project Manager
Ruthann Giusti, Medical Officer/Clinical Reviewer
Chana Fuchs, Product Reviewer
Ruth Cordoba-Rodriguez, Product Reviewer
Hong Zhao, Clinical Pharmacology Reviewer
Anne Pilaro, Pharmacology/Toxicology Reviewer
Kallapa Koti, Statistical Reviewer
Janet Barletta, Facility Reviewer (Drug Product)
Edwin Melendez, Facility Reviewer (Drug Product)
Michelle Clark-Stuart, Facility Reviewer (Drug Substance)
Jennifer Rouine, DDRE Reviewer
Lloyd Johnson, DSI Reviewer
Carole Broadnax, DDMAC Reviewer

Items covered:

1. **Milestones for Application Received on March 29, 2006:**
 - a. Committee Assignment: Complete
 - b. First Committee Meeting: Complete
 - c. Filing Meeting: Scheduled for May 10, 2006
 - d. Continued below under Dates Milestones Letters Must Issue

2. **Dates Milestone Letters Must Issue:**
 - a. Preclinical Discipline Review Letter: Due June 17, 2006
 - b. CMC Discipline Review Letter: Due August 29, 2006
 - c. Filing Action Letter: Due May 28, 2006
 - d. Deficiencies Identified Letter (74 day letter): June 11, 2006
 - e. Action Letter: September 28, 2006

3. **Upcoming Internal Team Meetings:**
 - a. Filing Meeting: Scheduled for May 10, 2006
 - b. Mid-Cycle Meeting: Scheduled for June 29, 2006
 - c. Labeling Meeting #1: Scheduled for July 12, 2006
 - d. Labeling Meeting #2: Scheduled for August 16, 2006
 - e. Labeling Meeting #3: Scheduled for September 6, 2006 *Will need to change this meeting based on ODAC Time/Date change.

Discussion During Meeting: Because the ODAC meeting has been changed to September 6, 2006, the review team agreed to combine this last labeling meeting with the post-ODAC debriefing meeting and the ODS safety conference. The RPM will revise the date and meeting agenda accordingly.

4. **ODAC (Tentatively Scheduled for September 12 and 13, 2006)**
Update: ODAC September 6, 2006:
- SGE Selection: ongoing
 - Competing Product List: ongoing
 - Practice Sessions for Presentations need to be scheduled for August and September 2006.
 - ODAC Tentative Timeline attached for September 6, 2006 meeting.
5. DSI Inspection update:

Indication	Protocol #	Site (Name of Clinical Investigator and Full Address)	Subject # at each site
Data Audit: Belgium	20020408	1103	N=63 (14%)
Data Audit: Italy	20020408	1401	N=34 (7%)
Data Audit: Belgium	20020408	1104	N=23 (5%)
Data Audit: Belgium	20020408	1102	N=21 (5%)

Discussion During Meeting: Final arrangements are being made, a field investigator has been identified and inspections should begin around June 8, 2006.

6. Manufacturing site inspection update:
- Amgen Thousand Oaks Facility: Inspection Date: 5/31/06-6/2/06
 - Inspection Date: 5/30/06-6/2/06
 - Abgenix: Inspection Date: 5/17/06
7. Amgen proposed: setting up weekly standing teleconferences between reviewers (clinical and CMC/facility)

Discussion During Meeting: Review team agreed to set up standing weekly teleconference times with Amgen beginning in early June. RPM will work with Regulatory contact at Amgen to establish these teleconference times.

Discussion:

8. Discuss any issues that have been identified during the review to date or need to request additional information:
- Pre-clinical
 - CMC
 - Facility
 - Clinical
 - Statistical
 - Clinical Pharmacology

Discussion During Meeting: Some issues were identified (pre-clinical identified missing fetal TK studies) (facility identified container/closure questions) and the review team decided to discuss with Amgen in a teleconference to request additional information.

CDRH agreed to follow up with RPM to identify a CDRH SGE to serve on the panel at ODAC. The SGE must be identified by May 18, 2006.

9. Do we have any questions for our consult reviewers at this time:

- a. DDMAC
- b. ODS/DDRE
- c. DSI
- d. ODS/DMETS: Currently reviewing trade name "Vectibix", ODS/DMETS has a 90 day review period (Consult given to them on 2/15/06). DDMAC (Katie Gray's Team) has forwarded along their review and they have no comments or concerns at this time.

10. Panitumumab Applications:

Discussion During Meeting:

11. Other Issues to be discussed as needed:

Discussion During Meeting: It is unclear to FDA if Amgen requested Accelerated approval. RPM will clarify with Amgen, and have Amgen formally request if it is not in the original BLA.

CPMS asked DMA who would lead the container/carton label review. It was decided the DBOP CPMS and RPM will review the labeling and consult as necessary DMA and DBOP review team members.

RPM reminded review team that the pediatric waiver and deferral request need to be addressed in the filing letter.

**BLA/NDA/PMA
Review Committee Assignment Memorandum**

STN: 125147/0

<input checked="" type="checkbox"/> Initial Assignment
<input checked="" type="checkbox"/> Change

Applicant: Amgen, Incorporated

Product: Panitumumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Monica Hughes	Reg. Project Manager	Admin/Regulatory	K. Jones	12-23-05
	Reviewer	Admin/Regulatory		
Chana Fuchs	Reviewer	Product*	P. Swann	12-23-05
Ruth Cordoba-Rodrigu	Reviewer	Product*	P. Swann	3-6-06
	Reviewer	Product		
Ruthann Giusti	Reviewer	Clinical	P. Keegan	12-23-05
	Reviewer	Clinical		
Hong Zhao	Reviewer	Clinical Pharmacology	H. Zhao	12-23-05
Anne Pilaro	Reviewer	Pharm/Tox	D. Green	12-23-05
Kallapa Koti	Reviewer	Biostatistics	M. Rothmann	12-23-05
Lloyd Johnson	Reviewer	BiMo	L. Ball	12-23-05
Jennifer Rouine	Reviewer	Safety Evaluator	S. Lu	1-10-06
	Reviewer	CMC, Facility*		
		Labeling		
		Other		
Janet Barletta	Reviewer	Facility	T. Harper-Velaquez	3-2-06

*add inspector, if applicable

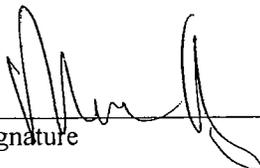
Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
Ann deMarco	Reviewer	Facility	T. Harper-Velaquez	1-5-06
Patricia Hughes	Reviewer	Facility	T. Harper-Velaquez	1-4-06

*reviewer types: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Monica Hughes
Name Printed


Signature

4-5-06
Date

Memo entered in RMS by:  Date: 4/7/06 QC by: _____ Date: _____



APR 27 2006

Amgen, Incorporated
Attention: Allesandro Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Cesano:

We have received your complete biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Our Submission Tracking Number (STN): BL 125147/0

Name of Biological Product: Panitumumab

Indication:

Date of Application: March 28, 2006

Date of Receipt: March 29, 2006

User Fee Goal Date: September 28, 2006

We will review this application under the provisions of 21 CFR 601 Subpart E – Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Unless we otherwise inform you, you must submit to us during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless we otherwise inform you, you must submit to us promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for patients 0-12 months for this application. We also acknowledge receipt of your request for a deferral of pediatric studies for patients 1 to 18 years for this application.

Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:

<http://www.fda.gov/oc/datacouncil/spl.html>.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biological Oncology Products

Office of Drug Oncology Products

Center for Drug Evaluation and Research

CONCURRENCE PAGE

RPM – Communication Screen Data Check

Letter Type: Acknowledgement Letter (ACK)

Summary Text: STN Assignment – Application

RPM – User Fee Data Check

Check “daily payment and arrears list” to see if payment has been received for this submission.

Fax User Fee cover sheet, with STN number, to Carla Vincent in RIMS.

RPM – Data Checks if Unacceptable for Filing due to Non-Payment of User Fees

Communication Screen: Add 2nd Letter Type (UN)

Submission Screen: In Arrears Box Is Checked

Milestone Screen:

Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped.

First Action Due Close Date And The New "UN" Entry Date Should Match

No Action Due Date

Original Submission Screen: Confirm STN Status – “Unacceptable for Filing”

cc: DBOP BLA File

R. Giusti

M. Clark-Stuart

J. Barletta

C. Fuchs

M. Hughes

A. Pilaro

H. Zhao

History: M. Hughes: 4-19-06: K. Townsend: 4.21.2006: 4.26.2006

File Name: N:DBOP\STN 2006\125147.0.3.ACK.doc

Division	Name/Signature	Date
OODP/DBOP	Monica Hughes	4/27/06
OODP/DBOP	Karen D. Jones	4/27/06
OODP/DBOP	P. Keegan	4-27-2006
OODP/DBOP	Kelly Townsend	4-27-06



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: April 5, 2006

FROM: Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of BLA application review status
Sponsor: Amgen, Incorporated
Product: Panitumumab
Indication: /

TO: BLA file STN 125147/0

The review status of this file submitted as a BLA application is designated to be:

Standard (10 Months)

Priority (6 Months)

Patricia Keegan, M.D.: Patricia Keegan Date: 4-5-2006



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 29, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: 125147/0/2: Acceptance Meeting CMC RU

FDA Attendees:

Monica Hughes
Lloyd Johnson
Michelle Clark-Stuart
Janet Barletta
Chana Fuchs
Ruth Cordoba Rodriguez
Patricia Keegan
Kaushikkumar Shastri
Hong Zhao
Kallappa Koti
Ruthann Giusti
Anne Pilaro

Discussion: This RU is acceptable.

Milestones: Disciple Review Letter for this RU is due by August 29, 2006.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 9, 2006
From: Monica Hughes, M.S., DBOP/OODP/CDER
Subject: 125147/0/2: First Committee Meeting CMC RU

FDA Attendees:

Monica Hughes
Lloyd Johnson
Michelle Clark-Stuart
Janet Barletta
Chana Fuchs
Ruth Cordoba Rodriguez (has been added to the review team)
Patricia Keegan
Kaushikkumar Shastri
Hong Zhao
Kallappa Koti
Ruthann Giusti
Anne Pilaro

Review team discussed milestones associated with this RU:

Review for Substantial Completion: April 28, 2006
Discipline Review Action: August 29, 2006

We discussed overall goals for the BLA:

1. 3 Hour Mid-Cycle will be held in June
2. Looking at ODAC in September, issue is data is for PFS, no data for OS
3. DSI will work with ORA to get foreign inspections completed by July 15, 2006.
4. Michelle Clark-Stuart is finalizing possible site inspection dates. Team will be going to Abgenix in Fremont, CA and Amgen's QC site at Thousand Oaks. Michelle will send out an email to team with inspection dates shortly.

Issues:

5. Follow up on who signs off on each Discipline Review and Letter.
6. CMC and Facility folks are having issues getting copies of the Biologic's MF from CDER's DMF room. We may have to request desk copies.

Follow-Up:

7. Set up Acceptance/Filing meeting for team



MAR 08 2006

Amgen, Incorporated
Attention: Allesandro Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Cesano:

We have received your presubmission of your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Our Submission Tracking Number (STN): BL 125147/0/2

Name of Biological Product: Panitumumab

Indication:

Date of Submission: February 24, 2006

Date of Receipt: February 27, 2006

We acknowledge receipt of this presubmission as a reviewable unit (RU) under the Continuous Marketing Application (CMA) Pilot 1 program. We also acknowledge your schedule for submission of the remaining portions of this application, as described in our meeting minutes of December 13, 2005, regarding BB-IND 8382. Our review clock will not start until the date on which you submit the final portion and inform us that your application is complete.

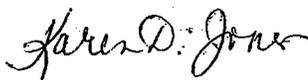
Unless we notify you otherwise within 60 days of our receipt date, we will accept each reviewable unit (RU) for review. We will provide preliminary review feedback on each individual, substantially complete, RU in a discipline review letter within six months of receipt.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, M.S., at (301) 796-2320.

Sincerely,



Karen D. Jones
Chief, Project Management Staff
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Acknowledgement Letter (ACK)
 Summary Text: CMA Acknowledgement

SS & RIS Data Check:

- If "Unacceptable for Filing" add 2nd LETTER TYPE "UN".
- Communication

RIS Data Check:

- Submission Screen: In Arrears Box Is Checked
- Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match
- No Action Due Date
- STN Status – Unacceptable for Filing

cc: DBOP BLA File
 R. Giusti
 A. Demarco
 C. Fuchs
 M. Hughes
 P. Hughes
 A. Pilaro

History: K. Townsend: 3.3.2006
 File Name: N:\DBOP\STN 2006\125147.0.2.ACK.doc

Division	Name/Signature	Date
DBOP/0000	<i>mg</i>	3-8-06
0000/DBOP	<i>Karen D Jones</i>	3-8-06
0000/DBOP	<i>Kelly Townsend</i>	2/10/06



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 2, 2006
From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP
Subject: 125147/0: Acceptance Meeting for 1st CMA Pilot 1 RU (pre-clinical)

Attendees:

Monica Hughes
Patricia Keegan
Martin Green
Ruthann Giusti
Anne Pilaro
Kaushikkumar Shastri

Discussion: First CMA Pilot 1 RU (pre-clinical) Received on 12-16-06.

Follow up from First Committee Meeting: Anne Pilaro stated that she was having technical issues accessing files accessing the primary data with an ".xpt" extension and would work with Mina Hohlen of OIM to see if the issue can be resolved.

Anne worked out this issue with the assistance of Mina Hohlen. There are no outstanding issues to prevent us from accepting this pre-clinical RU.

No letter will be sent to the sponsor as the acknowledgment letter for the RU had standard language incorporated stating that if they do not hear from us within 60 days to consider it accepted.

Milestones review: Disciple Review Letter for this RU is due by June 17, 2006.

APPEARS THIS WAY
ON ORIGINAL

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
OFFICE OF ONCOLOGY DRUG PRODUCTS
DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS**

**White Oak Office Complex – Building 22
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
FAX #: 301-796-2320**

FACSIMILE TRANSMISSION RECORD

3

TOTAL NUMBER OF PAGES: _____ (Including Cover Page)

FAX TO: Mary Celine-Scott, Ph.D., MBA, at Amgen Inc.

Facsimile Telephone No. (805) 480-1330 **Voice Telephone No.** _____

FROM: Monica Hughes, M.S., Regulatory Project Manager

Facsimile Telephone No. 301-796-9849 **Voice Telephone No.** 301-796-1371

DATE: 1-18-06 **TIME:** _____

MESSAGE: Mary,

Attached is a copy of the Acknowledgement Letter for the first BLA RU (pre-clinical) for

Panitumumab.

Please call me to confirm receipt of this facsimile.

Thank you,

Monica

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

I

2 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

Memorandum

Date: January 12, 2006
From: Monica Hughes, M.S., Regulatory Project Manager DBOP/OODP
Subject: 125147/0: First Committee Meeting for 1st CMA Pilot 1 RU (pre-clinical)

Attendees:

Monica Hughes
Patricia Keegan
Martin Green
Hong Zhao
Ruthann Giusti
Anne Pilaro
Kaushikkumar Shastri
Chana Fuchs
Lloyd Johnson

Discussion: First CMA Pilot 1 RU (pre-clinical) Received on 12-16-06.

Anne Pilaro stated that she was having technical issues accessing files accessing the primary data with an ".xpt" extension and would work with Mina Hohlen of OIM to see if the issue can be resolved.

Anne stated that the submission contains:

104 Primary toxicology reports
17 Secondary reports
3-4 PK reports
2 Comparability reports

Lloyd Johnson requested that Amgen submit clinical site information regarding the pivotal study completed in Europe. Specifically,

1. The total number of sites/ patient accrual per site
2. Verify that financial disclosure documentation is in order for all sites and to ask if any of the disclosures triggered interests.
3. Specific contact information at each site (name of main site contact, phone, fax, address).

**BLA/NDA/PMA
Review Committee Assignment Memorandum**

STN: 125147/0

<input checked="" type="checkbox"/> Initial Assignment <input type="checkbox"/> Change

Applicant: Amgen, Incorporated

Product: Panitumumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Monica Hughes	Reg. Project Manager	Admin/Regulatory	K. Jones	12-23-05
	Reviewer	Admin/Regulatory		
Chana Fuchs	Reviewer	Product*	P. Swann	12-23-05
	Reviewer	Product*		
	Reviewer	Product		
Ruthann Giusti	Reviewer	Clinical	P. Keegan	12-23-05
	Reviewer	Clinical		
Hong Zhao	Reviewer*	Clinical Pharmacology	H. Zhao	12-23-05
Anne Pilaro	Reviewer	Pharm/Tox	D. Green	12-23-05
Kallapa Koti	Reviewer	Biostatistics	M. Rothmann	12-23-05
Lloyd Johnson	Reviewer	BiMo	L. Ball	12-23-05
Jennifer Rouine	Reviewer	Safety Evaluator	S. Lu	1-10-06
Patricia Hughes	Reviewer	CMC, Facility*	T. Harper-Velaquez	1-4-06
		Labeling		
		Other		
Ann deMarco	Reviewer	Facility	T. Harper-Velaquez	1-5-06

*add inspector, if applicable

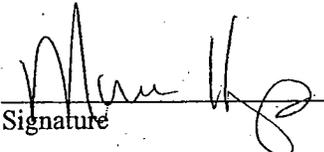
Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

*reviewer types: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Monica Hughes
Name Printed


Signature

1-10-06
Date

Memo entered in RMS by: Kx Date: 1/17/06 QC by: _____ Date: _____



JAN 11 2006

Amgen, Incorporated
Attention: Allesandro Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Cesano:

We have received your presubmission of your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Our Submission Tracking Number (STN): BL 125147/0

Name of Biological Product: Panitumumab

Indication: /

Date of Submission: December 15, 2005

Date of Receipt: December 16, 2005

We acknowledge receipt of this presubmission as a reviewable unit (RU) under the Continuous Marketing Application (CMA) Pilot 1 program. We also acknowledge your schedule for submission of the remaining portions of this application, as described in our meeting minutes of December 13, 2005, regarding BB-IND 8382. Our review clock will not start until the date on which you submit the final portion and inform us that your application is complete.

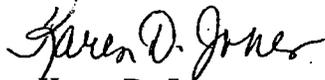
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Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, M.S., at (301) 796-2320.

Sincerely,



Karen D. Jones
Chief, Project Management Staff
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Acknowledgement Letter (ACK)
 Summary Text: CMA Acknowledgement

SS & RIS Data Check:

- If "Unacceptable for Filing" add 2nd LETTER TYPE "UN".
- Communication

RIS Data Check:

- Submission Screen: In Arrears Box Is Checked
- Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match
- No Action Due Date
- STN Status - Unacceptable for Filing

cc: DBOP BLA File
 R. Giusti
 A. Demarco
 C. Fuchs
 M. Hughes
 P. Hughes
 A. Pilaro

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DBOP/DBOP	<i>Allen Paulmond</i>	1-13-06



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 13, 2005
From: Monica Hughes, M.S., CDER/OODP/DBOP
To: IND 8382
Subject: Pre-BLA MTG, and discussion regarding the acceptability of the Panitumumab application into the CMA Pilot 1 Program

Meeting Date: November 22, 2005 **Time:** 1:00 PM-2:30 PM EST

Location: WO, Room 1417

Sponsor: Immunex Corporation

Product: Panitumumab ([Human Monoclonal Antibody (ABX-EGF) (Abgenix) to Epidermal Growth Factor Receptor] with and without Chemotherapy)

Proposed Use: —

Type of meeting: Pre-BLA

Meeting Purpose: To obtain agreement on the Panitumumab BLA submission as a Continuous Marketing Application under the Pilot 1 program and to reach agreement on the proposed content and presentation of the reviewable units. In addition, to reach agreement on any outstanding preclinical, immunogenicity, CMC, clinical, and clinical postmarketing commitment issues.

Note: Draft responses by FDA to Immunex's questions were faxed on November 21, 2005, and are incorporated below.

Revised Background Information From 11-21-05 Facsimile: Immunex originally intended to submit the results of Study 20030167, a Phase 2 single-arm study of single agent Panitumumab for 3rd/4th-line treatment of patients with EGFR expressing ($\geq 10\%$ of evaluated tumor cells) metastatic colorectal cancer (CRC) with progressive disease or relapse while on or after fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy, in support of accelerated

approval for Panitumumab. This version of the protocol, submitted as amendment 167 to BB-IND 8382, was accepted under a Request for Special Protocol Assessment in December, 2003, and following licensure of Cetuximab and of Bevacizumab in February, 2004, enrollment to this protocol was adversely affected.

In December, 2004, Immunex met with FDA to discuss the use of Study 20020408, [a two-arm, randomized, open-label trial comparing best supportive care (BSC) alone to BSC plus Panitumumab in 3rd/4th- line treatment of patients with EGFR expressing ($\geq 1\%$ of evaluated tumor cells) metastatic colorectal cancer (CRC) with progressive disease or relapse while on or after fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy to support approval. This ongoing study was conducted primarily in Europe. Based upon discussions with FDA, changes in the primary analysis population (from per-protocol to intent-to-treat), and reflected in revisions to the statistical analysis plan (SAP) resulted in a modification of the original sample size (from 600 to 430 patients). The trial was closed after accrual of 463 subjects. FDA agreed that Study 20020408, with a primary endpoint of progression-free survival (PFS) and secondary endpoint of overall survival (OS), was adequate in design to support accelerated approval based on an improvement in PFS or regular approval based on effects on PFS and on overall survival.

Study 20040249, entitled "A randomized open-label controlled, clinical trial of chemotherapy and Bevacizumab with and without Panitumumab in the first-line treatment of subjects with metastatic colorectal cancer" was submitted to the IND on February 17, 2005, and comments were provided April 15, 2005. FDA also provided comments on the deficiencies in the design of Study 20040249 and the development plan for Panitumumab.

On May 12, 2005, Fast Track designation was granted for Panitumumab for improvement in disease-free and overall survival in patients with CRC receiving first-line chemotherapy for metastatic disease, in study 20040249, and for improvement in progression-free survival, overall survival and objective tumor responses (complete response and partial response) in the treatment of metastatic colorectal cancer after failure of standard, irinotecan- and oxaliplatin-containing, chemotherapy regimens under study 20020408, entitled, "An Open-Label, Randomized Phase 3 Clinical Trial of ABX-EGF Plus Best Supportive Care Versus Best Supportive Care in Subjects with Metastatic Colorectal Cancer."

Immunex met with FDA on May 24, 2005, to discuss issues relevant to planning for a BLA submission. At this meeting, FDA re-iterated that an analysis of the effects on overall survival in Study 20020408 was necessary to support regular approval. FDA agreed that data from the single-arm, single agent Panitumumab trials in patients with CRC (Studies 20030167, 20030250 and 20025405) could be submitted as supportive of safety and activity. The potential for BLA submission under the CMC pilot 1 program was discussed. FDA clarified that

Immunex agreed to provide a series of exploratory analyses evaluating the relationship between EGFR expression and clinical outcomes. Immunex also agreed to provide FDA with a development plan to verify the clinical benefit of the

improvement in PFS and to support regular approval in the event that an improvement in overall survival was not demonstrated in Study 20020408.

On July 28, 2005, based upon clarification from Immunex regarding the intent of Study 20040249, FDA issued a revised letter for Fast Track designation. This letter noted that Study 20020408 was intended to support approval in

through demonstration of improvements in overall survival, progression-free survival, and objective tumor responses in patients receiving Panitumumab as compared to patients receiving best supportive care only.

In September 9, 2005, Immunex submitted an amendment to BB-IND 8382 containing a draft protocol for Study 20050181, entitled "A randomized, multicenter phase 3 study to compare the efficacy of Panitumumab in combination with chemotherapy (FOLFIRI) to the efficacy of chemotherapy alone in patients with previously treated metastatic colorectal cancer". This protocol was identified as the trial intended to verify clinical benefit of Panitumumab in support of regular approval in the event that an improvement in overall survival was not demonstrated in Study 20020408. FDA provided the following advice in a Nov. 8, 2005 letter to Immunex: "if a highly statistically significant effect on overall survival is demonstrated, with consistent evidence of benefit in meaningful subgroups, Study 20050181 could serve to support regular approval and could serve to verify the effects on the surrogate endpoint (PFS) demonstrated in Study 20020408." FDA also requested that the final protocol for Study 20050181, along with relevant documents (e.g., final statistical analysis plan) be submitted to FDA under a Request for Special Protocol Assessment.

Sponsor questions and FDA response:

Clinical Issues:

1. *Does the FDA agree that the progression free survival data and interim overall survival data from the pivotal study 20020408 (described in Appendix 8), in combination with data from the supportive colorectal cancer trials (20030167, 20030250, 20025405), adequately demonstrate safety and efficacy of Panitumumab in*

FDA Response Faxed on 11-21-05: *o. he progression free survival data and interim overall survival data from these studies do not support a regular approval. Although these data may support accelerated approval, FDA has concerns since the effects on PF do not appear to be predictive of an effect on overall survival benefit. herefore, these data will have to be thoroughly reviewed by FDA, li ely in consultation with DA . n order to consider accelerated approval in this situation it would also be important that a confirmatory study be significantly underway. Please submit the current schedule for initiating and conducting the confirmatory study and*

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address Immunex's ability to conduct the study should the product be approved prior to completion of the trial.

Discussion During Meeting: Immunex acknowledged that results from 20020408 did not show an effect on overall survival (), that this will not change with additional follow-up, and agreed to submit the confirmatory trial (20050181) in 2nd line m to the FDA in December 2005 under a request for Special Protocol Assessment.

Immunex noted that a draft synopsis for 20050181 was submitted to FDA in September 2005 and received comments from FDA in November 2005, and that those comments would be incorporated into the final protocol to be submitted in December 2005.

2. Immunex is examining the administration of Panitumumab over 30-min rather than 60-min, as described in Section 4.3.5.

FDA Response Faxed on 11-21-05:

Discussion During Meeting: Immunex agreed and had no further comments.

Previous Action Items:

3. Does the Agency have any comments or require clarification on the following action items from the 24 May 2005 Meeting:
 - a. Integrated Statistical Analysis Plans (iSAPs) for the clinical summaries of efficacy and safety were submitted 12 September 2005 (Serial No. 0411); the SAP for the population pharmacokinetic analysis was submitted 20 October 2005 (Serial No. 0432).

FDA Response Faxed on 11-21-05: The efficacy data (objective tumor response) from study 20020408 should not be pooled with results from studies 20030167 and 20030250 in an integrated analysis. Otherwise, the iSAPs for the clinical summaries of efficacy and safety are acceptable. Immunex's proposed data analysis plan for a population pharmacokinetic analysis of Panitumumab in subjects with cancers appears reasonable.

Discussion During Meeting: Immunex stated they accepted FDA's advice not to pool data but asked for clarification as to why this would not be acceptable.

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FDA stated that 20020408 was a randomized study with different cut-off points and that pooling of the data would pool disease assessment results determined using the IS criteria with results derived using other response criteria.

- b. *Synopsis of trial design for confirmatory trial (backup) (Study 20050181) was submitted 09 September 2005 (Serial No. 0410); the Special Protocol Assessment (SPA) package will be submitted before submission of first BLA module.*

FDA Response Faxed on 11-21-05: *Responses to Immunex's questions concerning the design of the current proposed confirmatory trial (Study 20050181) were faxed on November 8, 2005. FDA may have additional comments following review of the complete SPA submission but has no additional comments concerning the design of this trial at this time.*

Discussion During Meeting: *Immunex agreed and had no further comments.*

- c. *The pediatric plans are briefly described in this briefing document. A detailed proposal will be submitted prior to the final reviewable unit of the BLA.*

FDA Response: *As outlined, Immunex's proposals to seek a deferral for pediatric patients 12 months of age or older, to request a waiver for studies in patients less than 12 months of age, and to conduct a pediatric dose-finding study in children and adolescents with treatment refractory solid tumors with a subsequent Phase 2 study (if Panitumumab is found to be safe in children) are acceptable. FDA may have additional comments upon review of the protocols.*

Discussion During Meeting: *Immunex agreed and had no further comments.*

Nonclinical issues, Pharmacology:

4. *In the meeting 24 May 2005 FDA requested "tabular summaries of tumor volumes, body weights and any available data for serum levels of Panitumumab for the individual animals in each treatment group for each of the respective study reports". These data are not available for the original Abgenix studies, however they were tabulated for the later studies (see Section 6.1). Immunex proposes that this information be included in each study report, rather than a single integrated table for the 100+ studies. Does the FDA concur?*

FDA Response Faxed on 11-21-05: *Inclusion of the individual animal findings and summary tables of the tumor volumes, body weights, and serum Panitumumab levels into the individual study reports and a tabulated summary of all pharmacology studies in Module 2 of the electronic TD submission is acceptable.*

Discussion During Meeting: Immunex agreed to provide this information in Module 2 of the quality and had no further comments.

5. At the 15 September 2005 meeting, the FDA requested information concerning Immunex data clarifying the role of EGFr expression levels (as measured using an IHC assay) in the anti-tumor effect of Panitumumab. Although Immunex does not plan to make any label claims with respect to the predictive value of IHC in selecting subjects with tumors most likely to respond to Panitumumab, a brief description of our nonclinical data is included in Section 6.2 of this briefing document. Does the Agency have any additional questions on this topic?

FDA Response Faxed on 11-21-05: The BLA submission should contain the results of exploratory analyses assessing for correlations between EGF expression (the intensity of and/or proportion of tumor cells with EGFr membrane-expression) with the anti-tumor effect of Panitumumab. In addition, a detailed description of the methodologic approach used in the analyses and the primary data used to generate these analyses should also be contained in the BLA submission. Any studies that correlate expression by flow cytometric analysis (i.e., as was performed for several of the murine xenograft tumor models) with EGFr expression by immunohistochemistry staining should be specifically noted.

Discussion During Meeting: Immunex agreed to provide the EGF data and had no further comments.

Previous Action Items:

6. Does the Agency have any comments or require clarification on the following action items from the 24 May 2005 Meeting:
 - a. The six-month toxicology report will be submitted before 15 November 2005.

FDA Response Faxed on 11-21-05: Submission of the six-month toxicology report at the proposed date will not allow sufficient time for FDA to perform an adequate review of the data prior to either the upcoming pre-BLA meeting, or submission of the first reviewable unit of the BLA in December, 2005. Therefore FDA will defer any decision regarding the adequacy of this study to support market approval and labeling of Panitumumab until receipt and review of the CMA pilot unit for non-clinical safety.

Discussion During Meeting: FDA reiterated that the six month toxicology report was just received in the division and would not comment on the study during this meeting. Because longer term animal studies are not available, Immunex agreed to provide safety information from the clinical studies at the requested dose and schedule in patients

receiving Panitumumab for ≥ 6 and ≥ 9 months (see Immunex's attached slide presentation, slide 37).

Immunogenicity

7. The cross-study summary of immunogenicity is summarized in this briefing document (Section 5) and the draft report is included as Appendix 3. The final document, will be submitted before 15 December 2005. Does the FDA have comments on the structure and content of this document?

FDA Response Faxed on 11-21-05: FDA has the following comments/questions:

- a. Immunogenicity data, provided in SAS-compatible datasets, should include identification of the product administered (murine-versus CHO-derived product) and assay method(s) used as well as the reported result(s) for each subject. Identification of sampling times relative to study treatment day should also be included.

Discussion During Meeting: Immunex agreed to provide the final immunogenicity data in module 5 with the Efficacy in March 2006. FDA agreed this was acceptable.

- b. Please clarify whether samples testing positive for HAMA were identified by both the Abgenix and the Immunex assays. If all samples were tested using only one of the assays, please address the ability of the other assay to be as sensitive in the detection of HAMA.

Discussion During Meeting: Immunex agreed to clarify this in the quality portion of the BLA submission. FDA requested that validation of all the assays used for immunogenicity assessment be provided in the BLA submission. Immunex agreed to provide the validation of all assays in Module 3 of the quality

CMC Issues:

8. Does the Agency agree that the peptide map (Analytical Method No. A01531) and analytical method validation, that will be used to monitor product related impurities in the post approval stability program, may be submitted to the FDA during the review period of the CMC RU, no later than 31 March 2006?

FDA Response Faxed on 11-21-05: No, FDA does not agree. All CMC information should be submitted as a complete reviewable unit. In exceptional cases, a proposal to submit a portion of the RU separately will be considered based on compelling rationale.

Discussion During Meeting: Immunex agreed with the need to make the part of the original quality RU submission and agreed to provide this in the January 2006 quality RU submission.

9. Does the Agency agree that the additional stability data may be provided during the review period of the CMC RU, no later than 31 March 2006?

FDA Response Faxed on 11-21-05: Yes FDA agrees. Data from the additional stability time-points acquired after submission of the CMC RU should be submitted to the BLA in support of the requested expiration dating. However, the initial CMC RU submission should include all stability data available at the time of submission as well as validation of all stability assays.

Discussion During Meeting: Immunex agreed to provide information as proposed by FDA.

10. Does the Agency agree that _____ using actual processing equipment and areas of the facility that will be used for commercial manufacture of Panitumumab, would be acceptable for a pre-approval inspection at _____

FDA Response Faxed on 11-21-05: No, such a proposal is not acceptable to FDA. Please provide a justification as to why deviation from the standard approach is proposed.

Discussion During Meeting: Immunex stated they understood FDA's concern with the inspections utilizing _____ and agreed to re-work the manufacturing schedule so that a production run is occurring at the time of inspection. Immunex also agreed to provide updated manufacturing schedules in the quality RU in January 2006. FDA requested that the updated manufacturing schedules be submitted earlier than that if it is possible. Immunex agreed.

Regulatory Issues, USPI Presentation:

11. Immunex does not plan to include a draft USPI in the December submissions. The draft included with the final RU will be in the SPL format, as detailed in the "SPL Implementation Guide for FDA Content of Labeling Submissions", Version 2a, Revision 1, October 2005. If the Physicians' Labeling rule is issued at least 45 days prior to the final RU submission, the USPI will be presented in that new format; if the specifications are delayed, Immunex will provide a reformatted document during the review cycle. Does the Agency agree this approach is appropriate?

FDA Response Faxed on 11-21-05: This proposal is not fully acceptable to FDA.

The draft USPI must be submitted according to the latest version of the SPL Implementation Guide, and compliance with the implementation requirements of the final Physicians' Labeling rule are required. In addition, please provide USPI in word format with clean and annotated versions in the eCTD submission.

Discussion During Meeting: *Immunex requested clarification on two points. (1) Immunex is using the current version of SPL guidance to create the labeling and asked what FDA would expect if it was revised or modified just prior to submission. (2) Immunex asked whether they will be required to comply with the proposed Physicians' Labeling Rule if it is published the "day before" submission. FDA cannot comment on this scenario regarding the Physicians' Labeling Rule but stated that provisions in the rule should be in place to deal with such a situation. The final rule will be expected to have a reasonable implementation plan. FDA can discuss how to specifically address the new rule for this BLA after the rule publishes.*

FDA clarified that while SPL is required to be submitted based on guidance current at the time of submission that we request labeling negotiations between FDA and Immunex to occur in MS Word format, not in SPL; once agreement on final labeling is reached, Immunex will submit the final version in SPL. Immunex agreed.

12. *As requested at the 15 September 2005 meeting, the sections of the draft USPI for Panitumumab that relate to the role of patient selection by use of the DakoCytomation EGFR pharmDx™ kit are included in Appendix 4. Does the Agency have any comments on the proposed verbiage?*

FDA Response Faxed on 11-21-05: *No, FDA has no comments at this time.*

Discussion During Meeting: *Immunex agreed.*

Continuous Marketing Application:

13. *Does the Agency agree that the BLA for Panitumumab, as detailed in the complete Table of Contents (Appendix 2) will be included in the Pilot 1 Continuous Marketing Application Program?*

FDA Response Faxed on 11-21-05: *FDA is willing to consider submission of the BLA for Panitumumab under the Pilot 1 Continuous Marketing Application Program, however FDA does not agree with the current proposal for submission of contents of the reviewable units. Please see FDA's response to questions 8 and 15 regarding the quality CMA RU; this RU must be submitted as a complete reviewable unit for Immunex's acceptance into the Pilot 1 CMA program. In addition, Immunex should address FDA's responses to questions 7, 10, 11, 18, and FDA's comment 22.*

Immunex has agreed to submit the complete safety (non-clinical) CMA RU in December 2005, the complete quality (CMC) CMA RU in January 2006, and the complete efficacy (clinical) CMA RU in March 2006. Immunex may wish to reconsider the timing of submission of the quality CMA RU in order to ensure that it is complete at the time of submission.

Discussion During Meeting: *FDA stated that Immunex responses during the meeting were determined to adequately address FDA's comments in questions 7, 10, 11, 18, and FDA's additional comment 22. Taking this into consideration, Immunex asked whether FDA agrees that the Panitumumab BLA application would be included in the Pilot 1 Continuous Marketing Application. FDA agreed to accept the Panitumumab application under the Pilot 1 Continuous Marketing Application with the complete Safety Reviewable Unit to be submitted in December 2005, the complete Quality Reviewable Unit to be submitted in January 2006, and the Efficacy Reviewable Unit to be submitted in March 2006.*

14. *Does the Agency agree that the proposed contents of the Safety Reviewable Unit (overview in Appendix 1), planned for submission in December 2005, comprise a complete technical section which is appropriate for review?*

FDA Response Faxed on 11-21-05: *Yes, FDA agrees with Immunex that the proposed contents of the Safety Reviewable Unit will provide appropriate information for review of the nonclinical pharmacology and toxicology data.*

Discussion During Meeting: *Immunex had no additional comments.*

15. *Does the Agency agree that the proposed contents of the Quality Reviewable Unit (overview in Appendix 1), planned for submission in December 2005, comprise a complete technical section which is appropriate for review?*

FDA Response Faxed on 11-21-05: *No, FDA does not find this acceptable. The proposed Quality RU presented in Appendix 1 does not include module 3.2.A. Please add this to the Quality RU for completeness of the unit.*

Discussion During Meeting: *Immunex agreed to provide module 3.2.A in the quality RU.*

16. *Does the Agency agree that the proposed contents of the Efficacy Reviewable Unit (overview in Appendix 1), planned for submission in March 2006, comprise a complete technical section which is appropriate for review?*

FDA Response Faxed on 11-21-05: *Yes, FDA agrees that the proposed contents of the Efficacy Reviewable Unit planned for submission in March 2006, comprise a*

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complete technical section which is appropriate for review.

Discussion During Meeting: Immunex had no additional comments.

Previous Action Items:

17. Does the Division have any comments or require clarification on the following:

- a. The FDA meeting with Immunex and DakoCytomation which was held 15 September 2005.

FDA Response Faxed on 11-21-05: Please see FDA's response to comment 4.

Discussion During Meeting: FDA clarified the mistake in the draft comments faxed on 11-21-05. It should have read "Please see FDA's response to comment 5". Immunex had no additional comments.

- b. The information provided for the FDA meeting with Immunex and which was planned for 12 October 2005.

FDA Response Faxed on 11-21-05: Draft comments were provided prior to the meeting which was scheduled for October, 12, 2005. Since Immunex cancelled the request for this meeting, these minutes serve as FDA's final comments. FDA has no additional comments at this time.

Discussion During Meeting: Immunex had no additional comments.

- c. The demonstration of the proposed electronic tools for submission and archival of radiological images which will be conducted at the FDA in early November 2005.

FDA Response Faxed on 11-21-05: The proposed approach presented by and Immunex during the meeting held on November 17, 2005, which demonstrated the proposed electronic tools for submission and archival of radiological images for the upcoming Panitumumab BLA submission, is acceptable. It is FDA's understanding that the following will be submitted as part of the radiological component simultaneously with the efficacy CMA RU:

- (a) A full set of the radiological images obtained for studies 20020408, 20030167, and 20030250. FDA is particularly interested in the 33 patients from the control arm of Protocol 20020408, crossed over to study 20030194, for whom there were discrepancies between the local

radiologists' and the — reviewers' determination of disease progression at the time of cross-over. Immunex has committed to provide additional images, reviewed centrally by — for these 33 patients that were obtained during treatment under Protocol 20030194.

Discussion During Meeting: Immunex agreed to provide this information and had no additional comments.

- (b) Radiological images reviewed only by local radiologists (not — , for all other patients (other than the 33 patients described above) enrolled in study 20030194 will also be provided in the BLA.

Discussion During Meeting: Immunex did not intend to provide this information to FDA. Immunex stated there are films for the 33 patients, however, only the responders (n = 17) would be digitized for FDA review. FDA stated further internal discussion would be necessary and asked Immunex if FDA could clarify this after discussions with DMIHP. Immunex agreed.

- (c) Immunex has some images for study 20025405 available; however, this study utilized the 2.5 mg/kg IV dose in hybridomas and were collected and analyzed at a later date. Immunex agreed to provide these images upon request but not to include them as part of the submission.

Discussion During Meeting: Immunex stated they are looking into the logistics of digitizing these films and are not sure at this time how quickly they can respond to an FDA request. Immunex agreed to get back to FDA.

- (d) Immunex will submit SAS-compatible datasets corresponding to the imaging database, by study and as an integrated dataset. For each patient, the database will contain the Patient ID, protocol number, treatment assignment, results of the local study site interpretation and the central interpretation for each protocol-specified time-point for which radiological assessment was to be performed. These datasets will be provided in module 5 of the efficacy CMA RU eCTD submission. The read sheets should be submitted as pdf files. These pdf files should be hyperlinked to the line listings for radiologic readings at — contained in Module 5.

Discussion During Meeting: Immunex agreed to provide this information and had no additional comments.

Proposed Post Marketing Commitments:

18. Immunex proposes that information on the following topics will be submitted after the approval of Panitumumab. Does the FDA have any comments or concerns?

- a. Primary analyses of overall survival (OS) data from Study 20020408.

FDA Response Faxed on 11-21-05: Since the interim data analysis from Study 20020408 appears to preclude a survival advantage, FDA requests that the interim analysis of overall survival be submitted at the time of the initial BLA submission.

Discussion During Meeting: Immunex agreed to provide this in the complete Efficacy RU in March 2006.

- b. Additional analyses of the impact of EGFR status, as measured by the DakoCytomation EGFR pharmDx™ kit, on the efficacy of Panitumumab, incorporating final data from two duplicate single arm trials conducted in subjects whose tumors express EGFR (20030167, greater than or equal to 10% of evaluated tumor cells) and subjects whose tumors express low or negative EGFR (20030250, 9% of evaluated tumor cells or less) by the IHC kit. If feasible, data from additional Development and Medical Affairs trials conducted in colorectal cancer subjects who were not selected on the basis of EGFR status may be included in these analyses. If the results impact the use of the DakoCytomation EGFR pharmDx™ Kit, .

FDA Response Faxed on 11-21-05: FDA is willing to consider review of such data if it can be determined that the data derive from adequately designed and conducted studies. Agreement is contingent upon submission of information regarding the design and conduct of these additional trials and FDA's determination that the source of the data and the extent of the data are sufficient to fulfill the intent of the post-marketing commitment. Alternatively, additional studies and sources of data would need to be identified. In addition, discussion would be needed regarding the acceptability of the proposed analytic approach.

Discussion During Meeting: Immunex stated that interim response data from an

FDA also expressed interest in seeing data from the “PASTE” and “Medical Affairs” trials, and advised care in any definition of EGFR “negative” result since such a result might depend on how aggressively staining is sought.

Immunex agreed to work on a,

- c. If the OS results of Study 20020408 do not demonstrate the clinical benefit of Panitumumab, because of the cross-over study design Study 20050181, entitled, “A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer”, will be provided as a backup confirmatory trial for this approval. During the design of this trial, Immunex will seek FDA input on strategies for identification and validation of biomarkers that might serve as predictive markers for Panitumumab.

FDA Response Faxed on 11-22-05: FDA strongly recommends that the confirmatory study 20050181 be submitted for review under a Request for Special Protocol Assessment.

Discussion During Meeting: Immunex agreed to submit the confirmatory study 20050181 under a Request for Special Protocol Assessment.

- d. Conduct of Phase 1 and Phase 2 pediatric studies designed with input from the Agency.

FDA Response Faxed on 11-22-05: No response in draft comments faxed on 11-22-05.

Discussion During Meeting: Immunex indicated that the Phase 1 study would be submitted to IND 8382, prior to the first RU module submission in December 2005.

Additional Discussion Items:

Additional FDA Questions/Comments Faxed on 11-21-05:

19. Please provide validation of the immunogenicity biacore assay as part of the quality CMA RU submission.

Discussion During Meeting: Immunex agreed to provide this information in the regional appendices in Module 3 of the Quality RU.

20. Panitumumab drug product seems to contain “translucent to white amorphous proteinaceous particles that are removed by an in line filter during infusion”. Please be sure to include information regarding identification of the particles, conditions that lead to increased particle formation, and kinetics of formation in the quality CMA RU submission. Additionally, studies showing the ability of the inline filter to remove these particulates and not clog the filter, as well as deliver appropriate amounts of drug to the patient should be included. These studies should be conducted using representative lots of Panitumumab drug product at or beyond the requested expiration dating as well as analysis with lots stressed to assess worst case situations. A quantitative assay to measure these particulates in drug product should be developed and will be required in support of any future changes in the formulation process.

Discussion During Meeting: Immunex agreed to provide this information in Module 3 of the Quality RU. Immunex asked FDA to clarify that the last sentence above is referring to any post-approval, if any changes are made to assess particulate levels. FDA stated yes.

21. Those programs used to create the derived datasets from the raw datasets should be included in this BLA submission. If these programs are not submitted and the FDA analyses based on the raw data lead to different results from those submitted results, the official results will be those from the FDA analyses. Please include this information as part of the efficacy CMA RU submission.

Discussion During Meeting: Immunex agreed to provide this information in the Efficacy RU in March 2006.

22. The efficacy CMA RU module, should contain the information that Immunex agreed to provide in the May 24, 2005 meeting, specifically the exploratory analyses of the relationship between EGFR expression and clinical outcomes. In order to allow integration of information across studies, the primary data should be provided, in a SAS-compatible dataset, for each patient, as follows: Patient ID, protocol, treatment assignment, the drug efficacy information (tumor response assessment, date of progression, date of death), and baseline entry EGFR expression data. At a minimum,

EGFr expression data should include the percentage of tumor cells with membranous staining (please provide specific result reported rather than ranges) and highest staining intensity reported (1+ through 3+). If available, Immunex may also report the percentages of tumor cells with 1+, with 2+ and with 3+ membranous staining for each subject. For all analyses, please provide detailed information on the methodologic approach used (e.g., statistical test, assumptions used, handling of missing data) in sufficient detail to permit FDA to replicate these analyses using the dataset provided in the submission.

Discussion During Meeting: *Immunex agreed to provide this information in Module 5 of the Efficacy RU in March 2006. Immunex confirmed the programs will be provided as well.*

Decisions/Agreements Reached: *FDA accepted Immunex's proposal for the Panitumumab BLA application to be included in the Pilot 1 Continuous Marketing Application program and for the reviewable units to be submitted on the following timeframe:*

- (1) The complete Safety RU will be submitted to FDA in December 2005,*
- (2) The complete Quality RU will be submitted to the FDA in anuary 2006, and;*
- (3) The complete Efficacy RU will be submitted to the FDA in March 2006.*

Attachments: *Immunex's slide presentation.*

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FDA Attendees:

*Center Drug Evaluation and Research
Office of New Drugs
Sally Loewke, M.D.*

*Center Drug Evaluation and Research
Office of Oncology Drug Products
Glen ones, Ph.D.
Karen eiss, M.D.*

*Center for Devices and Radiological Health
Nina Chace, M.S.
Robert Becker, M.D., Ph.D.
Francis Kalush, Ph.D.
Gene Penello, Ph.D.*

*Office of the Commissioner
Office of Combination Products
Patricia Love, M.D.*

*Office of Oncology Drug Products
Division of Biological Oncology Products
Monica Hughes, M.S.
Karen ones
Patricia Keegan, M.D.
Ruthann Giusti, M.D.
oshua Bilenker, M.D.
oseph Gootenberg, M.D.
Anne Pilaro, Ph.D.*

*Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation 5
Hong hao, Ph.D.*

*Office of Biotechnology Products
Division of Monoclonal Antibodies
Chana Fuchs, Ph.D.*

*Office of Pharmaceutical Sciences
Division of Quality Assurance
Gupreet Gill-Sangha, Ph.D.
Jianming Li, Ph.D.*

Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics
Biological Therapeutics Statistical Staff
Mark Rothmann, Ph.D.

Sponsor Attendees:

Immunex Corporation:

Alessandra Cesano, MD Senior Director, Regulatory Affairs
Lynn Navale, MS Senior Biostatistician, Biostatistics
Sharon Baughman, PhD Director, Pharmacokinetics Drug Metabolism
Richard L. Phillips, PhD Director, Regulatory Affairs
Jeff Engelhardt, DVM, PhD, DACVP Senior Director, Toxicology Pathology
Robert Radinsky, PhD Senior Director, Research Oncology
Jennifer Gansert, MD, PhD Clinical Scientist, Oncology Development
Mary Celine Scott, PhD, MBA Senior Manager, Regulatory Affairs
Peggy Lum, BS Associate Scientist, Pharmacokinetics Drug Metabolism
Sophie Visonneau, PhD Associate Director, Oncology Development
Jennifer Mercer Associate Director, Regulatory Affairs CMC
Steve Swanson, PhD Senior Director, Clinical Immunology
Barbara Mounho, PhD, DABT Principal Scientist, Toxicology
Michael Wolf, MS Associate Director, Biostatistics
Michael Mullenix, PhD Principal Scientist, Clinical Immunology
Robert Radinsky, Ph.D.
Donna Peterson

Abgenix:

Anice Castillo, BS Vice President, Regulatory Affairs
Gisela Schwab, MD Chief Medical Officer

DakoCytomation:

Tiffany Almeroth, RAC Manager, Regulatory Affairs

Teleconference Date: October 12, 2005 Time: 2:00 PM-3:00 PM EST

Sponsor: Immunex Corporation

Product: Panitumumab [Human Monoclonal Antibody (ABX-EGF) (Abgenix) to Epidermal Growth Factor Receptor] with and without Chemotherapy

Proposed Use: —

Teleconference Purpose: To review a proposal for the submission and archival of independently-read radiological images and associated case report/review forms in support of the Panitumumab BLA submission.

Note: These are draft responses faxed by FDA to Immunex, Corporation on October 5, 2005..

Sponsor Questions and FDA Response:

1. *Does the Division agree with the proposal for providing independently-read radiological images and related case report/review forms for this submission?*

FDA Response: Yes; FDA agrees that the following proposal is acceptable:

- Submission of all radiologic images and all case report/review forms to verify pre-study eligibility for studies 20020408, 20030167, and 20030250 in the application, with Immunex's commitment to provide the same information for pre-study eligibility confirmation for study 20025405 upon request.
- Submission of radiological images and radiological case report/review forms to confirm tumor status during treatment for studies 20020408, 20030167, 20030250 and a subset from 20030194
- Submission of oncology assessment case report forms for 20020408, 20030167, and 20030250.

2. *Does the Division agree with the proposal for archival of these records?*

FDA Response: Yes, FDA agrees with Immunex's proposal.

3. *Does the Division have any additional questions with respect to the submission of independently-read radiological images and related case report/review forms for this submission?*

FDA Response: FDA requests that Immunex submit the following components in the original BLA submission as a separate section, related to the radiographic dataset, in the eCTD:

1. An Executive Summary of the radiographic data for each clinical trial (A description of the clinical trial protocol as it relates to the imaging data in the application, i.e., imaging acquisition procedure, response assessment criteria used, time points for radiographic evaluation, statistical plan integrated to radiographic data analysis and how missing data is handled).
2. Patient listings both in tabular summary and in Excel spreadsheet document for each study. The database should document the following for each study:
 - Patient ID number
 - Study treatment assignment
 - For each protocol specified time point, indicate whether image was obtained (yes/no)
 - Date of progression
3. — Project Tracking Database: should contain a tabular summary format and SAS dataset of listing of patients and their corresponding films by time point. The database must document the following:
 - Patients submitted to the database.
 - The radiographs submitted for each patient for each time point.
 - The completeness of the radiographs submitted for each patient for each time point.
 - The documentation of the sponsor's reported reason for each missing item in the database.
4. "Exceptions" Database documenting the reason for missing image sets. The database must document the following:
 - The reported reason why a radiological imaging assessment was not performed for each individual patient for each study protocol as compared to the actual enrolled patients in the clinical trial.
 - The reported reason why any radiograph or independent radiographic report for any designed diagnostic imaging time point is missing.

5. A copy of the Independent Review Charter.
6. Financial Disclosure Forms for all Independent Readers

Please note that elements # 2, # 3 and # 4 above should be provided in a Tabular Summary Format in the original BLA submission. Elements # 3 and # 4 should also be provided in SAS Dataset Format in the original BLA submission.

4. *Clarification is requested from the project team at FDA regarding the need to submit a demonstration of the imaging database approximately 6 months before the intended submission for planning purposes; this has been requested in support of other submissions.*

FDA Response: Prior to the actual submission of the BLA, Immunex Corporation is encouraged to contact the regulatory project manager for this application to request a meeting to discuss the technical requirements and format of the imaging portion of this application. This demonstration should be conducted prior to the pre-BLA/CMA Pilot 1 meeting.

**APPEARS THIS WAY
ON ORIGINAL**

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9 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Food and Drug Administration
Rockville, MD 20852

JUN 23 2005

Our Reference: BB-IND 8382

Amgen, Incorporated
Attention: Mary Celine Scott, Ph.D., M.B.A.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Scott:

Please refer to your **Investigational New Drug Application (IND)** for "Panitumumab [Human Monoclonal Antibody (ABX-EGF)(Abgenix) to Epidermal Growth Factor Receptor]" and to the meeting held on May 24, 2005, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,



Dale Slavin, Ph.D.
Regulatory Project Manager
Division of Review Management, and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

CONCURRENCE PAGE

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MEETING SUMMARY ENCLOSED (MS)

Concurrence box

Division	Name/Signature	Date
DAMP		6-23-05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

JUN 23 2005

Date: June 23, 2005
From: Dale Slavin, Ph.D., RPM ODE VI/DRMP/DTBOP
Subject: ADDENDUM to May 24, 2005, Meeting Minutes
To: IND 8382

Please refer to FDA's meeting minutes issued June 23, 2005, regarding the May 24, 2005, meeting. This is a follow-up addendum to those minutes regarding follow-up to questions 9 and 11, and action items 1 and 7.

FDA responded to these question 9 and item 1 by facsimile on June 7, 2005. A copy of that facsimile is included for your records.

FDA has the following comment regarding question 11 and item 7:

Please be advised that FDA will require data from nonclinical studies to demonstrate the safety of chronic administration of Panitumumab. As discussed at our meeting of May 24, 2005, FDA will require nonclinical studies in an appropriate animal model treated with Panitumumab for a 9-month duration, as specified in the ICH Guidance for Industry S4a. FDA agrees to review the data from the 6-month toxicology study of Panitumumab in non-human primates (Study #103917) as part of the original BLA submission, and to work with Amgen to devise appropriate language for labeling pending completion of the 9-month animal study.

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: JUN 23 2005
From: Dale Slavin, Ph.D., RPM, ODEVI/DRMP/DTBOP 
To: IND 8382
Subject: Type C meeting Clinical/Preclinical

Meeting: May 24, 2005 Time: 3:30 to 5:00 pm

Location: Woodmont Office Complex 2 6th Fl Conference Room G

Meeting Requestor/Sponsor: Immunex Corporation

Product: Panitumumab [Human Monoclonal Antibody (ABX-EGF)(Abgenix) to Epidermal Growth Factor Receptor]

Proposed Use:

Type of meeting: Type C

Meeting Purpose: To discuss the proposed/planned data (safety and efficacy) analyses for Panitumumab for the BLA submission to be submitted December 2005.

FDA faxed preliminary comments to Amgen on May 23, 2005. Those comments are included within the minutes (below), as well as any further discussion during the meeting of those faxed comments.

Sponsor questions and FDA response:

Clinical Efficacy Data

1. ***Does the Agency agree with the proposals in Section 5.2 of the briefing document for provision of efficacy data to support the target indication and US prescribing information?***

FDA Faxed Response:

With regard to the proposed target indication and labeling information, FDA has the following comments

- The studies to be provided support an indication that is restricted to metastatic, EGFR-expressing, colorectal carcinoma, as reflected by the eligibility criteria for the clinical studies.
- The target indication should include a more specific description of the indicated population,
- The studies providing primary support for efficacy were limited to a dose and schedule of 6 mg/kg every 2 weeks. There are no data to support the effectiveness of in product labeling. The adequacy of the data to establish the safety and efficacy of is a review issue.

Further Discussion:

Amgen agreed to take FDA's faxed comments (above) into consideration.

2. ***Does the Agency agree with the proposed approach to analyses of efficacy data discussed in Section 5.2.1?***

FDA Faxed Response:

The overview provides insufficient detail to address this question. In general, FDA considers the analyses of results according to the pre-specified analysis plan, as described in the clinical protocol or a separate statistical analysis plan document, to be the primary analysis for each of the specified protocol objectives.

In addition, to the pre-specified analyses, FDA requests a description of the exploratory analyses for primary and key secondary efficacy endpoints in each study of colorectal cancer according to the level of EGFR expression. The subsets for EGFR expression should be as described in the revised study 200408.

Further Discussion:

Amgen presented slides and clarified that they were proposing to perform an integrated analysis by pooling the results from their 5 monotherapy studies of

overall response and response duration from their studies as presented in the December 2004 briefing document, and that their plan would be to use two different analysis sets: all patients enrolled, and an adjudicated set of 250 patients with low or no EGF receptor. Regarding 20020408, Amgen is planning an analysis to examine the intensity of EGFR staining ($<3+$ versus $>3+$) and percent of cell membrane staining ($1-9%$ and $\geq 10%$) positive for EGFR.

3. *Primary survival data from the pivotal study, 20020408, are anticipated to be available during the license application review period (anticipated end April 2006). Does the Agency agree that submission of these data during the license application review will not be considered a major amendment?*

FDA Faxed Response:

No. This would be considered a major amendment under the standard review clock. As stated in the December 6, 2004 meeting minutes, analysis of overall survival is necessary to support regular approval, and the submission will not be considered complete without these data. However, FDA would consider a proposal for submission of reviewable units under a CMA Pilot 1. Under CMA Pilot 1, these data may be considered as a reviewable unit. Be advised that if the development program does not continue to meet the criteria for Fast Track designation, the Agency may choose to revoke Fast Track designation.

Further Discussion:

Amgen acknowledged and understood FDA's comments. Amgen stated that they do intend to file for accelerated approval and will submit a supplement for regular approval. If they were unable to meet the accelerated approval endpoints, Amgen stated that they did have a backup plan that they would share with FDA at the preBLA meeting that would be requested in the early 3rd quarter of 2005. Amgen confirmed that they are considering submitting a CMA pilot 1 request.

Clinical Safety Data

4. *Does the Agency agree with the proposals in Section 5.3 to provide integrated safety data to support the target indication in the license application?*

FDA Faxed Response:

Please see comments above regarding narrowing of the proposed indication. The proposal to combine and summarize safety data in Module 2.5.5 for the 4 specified groupings on page 47/107 is acceptable.

Further Discussion:

Amgen agreed to FDA faxed comments (above) and would submit the information once the data became available.

Does the Agency agree with the proposed approach for analyses of safety data discussed in Section 5.3?

FDA Faxed Response:

Additional analyses may be requested, based upon either data presented at the pre-BLA meeting or based upon FDA's review and assessment of the primary safety and efficacy studies. At the pre-BLA meeting, an overview of the preliminary assessment of safety findings and a description of the content and format of the application [e.g., detailed listing of the variables to be included and format of the SAS dataset] should be provided. The ultimate decision regarding need for additional analyses will be based upon review of the complete study results.

At this time, FDA requests that the following additional analyses be performed:

- An analysis of safety according to cell-line used to manufacture the final product (hybridoma vs. CHO cells); and,
- An analysis of monotherapy according to dose and schedule (2.5 mg/kg q wk vs. 6 mg/kg q 2wks vs. 9 mg/kg q 3 wks) in patients, regardless of tumor type, who received panitumumab monotherapy.

Further Discussion:

Amgen agreed to FDA's position and they would provide the above analyses requested by FDA.

6. *Does the Agency agree with the proposed approach for analyses of immunogenicity data proposed in Section 5.4.1, and the details of reanalyses discussed in Section 5.4.2?*

FDA Faxed Response:

The proposed approach is very general and although it appears reasonable, FDA cannot address this question until the immunogenicity protocol and the assay validation are reviewed.

Further Discussion:

Amgen clarified that they are developing an integrated immunogenicity report and that they are willing to share this report in advance with FDA. Amgen would be reanalyzing the immunogenicity studies utilizing an 'improved' assay. FDA and Amgen agreed that a follow up telecon to discuss the immunogenicity report, once the validation of the assay with the adequate detail are available, would be acceptable.

Due to the lack of standard regulatory methods for the assessment of infusion reactions, Immunex Corporation proposes reporting 3 types of analyses, which are detailed in Section 5.3.3.2. Does the Agency agree these analyses are appropriate and adequate?

FDA Faxed Response:

The approach appears reasonable.

Further Discussion:

FDA reiterated that the approach was probably reasonable but that FDA wanted to have clarity regarding the MedRA terms that are to be used. Amgen agreed.

Clinical Datasets

8. *Does the Agency find the content and analyses for the proposed 120-day update (Section 5.8) to be appropriate?*

FDA Faxed Response:

There is insufficient information regarding the specific contents of the update to the address the question. In addition, confirm that the 120-day safety update will include an updated ISS, which integrates the previously submitted data and all new information in the relevant sections and datasets of the ISS in the initial submission.

Further Discussion:

Amgen confirmed that they would provide an updated integrated safety report. Amgen stated that there was no new safety data from those studies recently initiated. Safety data will come from those studies that are to be submitted with the initial BLA submission. FDA agreed that this was acceptable. Amgen stated that they had submitted revised safety data cutoffs and FDA agreed to review those revisions and send their comments to Amgen in writing.

9. *Table 5-8 provided in this briefing document summarizes the proposals for provision of datasets, CRFs, and radiographic images for the clinical studies that are part of the license application. Does the Agency agree with these proposals?*

FDA Faxed Response:

Insufficient detail is included in the briefing document to address this question. This question will be re-assessed at the time of the preBLA meeting.

Further Discussion:

Amgen stated that they had revised table 5-8 per their fax of May 17, 2005. FDA stated that the revised proposal appeared reasonable but that FDA would get back to Amgen with a complete answer.

[please see attached addendum]

Amgen confirmed that all CRFs will be provided and that individual SAE reports including narratives and the translations of the narratives for the Japanese studies would be submitted. In addition, premature withdrawal would be included with the SAEs.

Amgen requested that FDA's response to the revised table occur rapidly and FDA stated that they would attempt to respond quickly.

10. *Immunex Corporation can provide the radiographic scans to the Agency via a number of varying formats ranging from submission of an entire validated system (computer and hard drives) containing all images and measurements exported from the central imaging facility repository to remote auditing by the Agency or a designated third party auditor over the Internet, as described in Section 5.2.2. Does the Agency have a preference as to the format they wish to receive these data for their review?*

FDA Faxed Response:

FDA requests that the radiographs for the controlled clinical trial (Study 20020408) be submitted under the proposal outlined in option 3 of the submission package (external hard drive submission). FDA encourages Immunex to request a separate teleconference call or site-visit to discuss the technical requirements for the submission of the radiographic dataset.

Further Discussion:

Amgen understood that FDA prefers the option #3, and Amgen will set up a site visit to determine the technical requirements.

Preclinical Safety

11. *Does the Agency agree that the proposed preclinical data: pharmacology (Section 6.1), pharmacokinetics (Section 6.3) and toxicology (Section 6.4) to be presented in the license application are sufficient to support approval in the proposed indication?*

FDA Faxed Response:

No. The toxicities that are observed in cynomolgus monkeys treated for 13 weeks in toxicology study #103917 included dose-dependant diarrhea and skin rash. Similar dermatologic and gastrointestinal toxicities have been observed with a related, licensed product that also inhibits the activity of this receptor, and are included in the WARNINGS section of the label. Taken together, these data suggest that the dermatologic and gastrointestinal effects seen with both Panitumumab and the related product are cumulative toxicities, and are related to the pharmacologic action, *i.e.*, inhibition of the biologic activity of the epidermal growth factor receptor. To address the potential cumulative toxicities associated with long-term Panitumumab exposure, FDA will require that Immunex provide data from nonclinical studies in an appropriate animal model treated for a 9-month duration, as specified in the ICH Guidance for Industry S4a, "Duration of Chronic Toxicity Testing in Animals (Rodent and Non-

rodent Toxicity Testing).” These data may be obtained by extending treatment in the ongoing, repeat-dose toxicology study #103419 in cynomolgus monkeys, or may be provided from the results of a separate, stand-alone toxicology study in cynomolgus monkeys.

Further Discussion:

Amgen stated that the non-human primate (NHP) toxicology study design had been previously agreed upon, and in addition greater than 65 patients have been treated for ≥ 6 months and greater than 33 patients have been treated for ≥ 9 months. They had concerns that there would be unnecessary exposure to animals. FDA explained that new data had become available after the agreement on study design in 2003, and that FDA was requiring 9 month toxicology data for all products of this class. The data derived from these studies would become part of the label similar to the data within the label of the precedent product. FDA stated that if the 9 month toxicology study were not finished at the time of filing this would be acceptable and that the study could be completed as a post marketing commitment or as a reviewable unit under the CMA Pilot 1 program.

Amgen suggested that

FDA stated that this proposal would require further internal discussion.

FDA requested that Amgen submit the final study report for the NHP toxicology studies. In addition, FDA agreed to consider the clinical study data for patients treated for ≥ 6 months, but advised that the clinical exposure data might be insufficient.

Regulatory Items

12. *Does the Agency agree that a pediatric deferral will be granted (Section 4.4)? Does the Agency agree the proposed datasets and analyses (Section 4.4) will meet the requirements of the geriatric rule?*

FDA Faxed Response:

Although it is likely a pediatric deferral may be granted, there is insufficient information concerning the plan for clinical development in the pediatric population (including timelines, study design(s) and age ranges to be studied) to address this question. Please provide this information in advance of submitting the BLA, and preferably prior to the pre-BLA meeting. A request for deferral of pediatric studies should be submitted in the BLA and the timeline for conducting and completion of the deferred pediatric studies should be provided.

There is insufficient information to address the question of the geriatric rule however the general approach described in Section 4.4 appears reasonable

Further Discussion:

Amgen agreed that they would formally request a deferral and would provide a plan for initiating pediatric studies with FDA. Amgen requested that FDA provide feedback on the proposed plan and deferral prior to the preBLA meeting. FDA agreed to attempt to hold a telecon (the telecon would be dependent on competing FDA priorities and schedules) to discuss the pediatric plan and recommended to Amgen that the plan should explore pediatric tumors that are EGFR positive, and that Amgen examine any correlation between expression and treatment response.

FDA asked Amgen if there were any specific toxicity issues and Amgen replied, that no there were not.

Amgen acknowledged FDA's comment regarding the geriatric rule requirements.

13.

14. *Immunex Corporation plans to include full copies of all references cited in Module 2 summaries and overviews, and pertinent references cited in other Modules. All other*

references will be available to the Agency upon request. Does the Agency agree with this approach (Section 4.5.1)?

FDA Faxed Response:

Yes, this is acceptable.

Further Discussion:

Amgen accepted FDA's response.

15. *The panitumumab license application is targeted for submission in December 2005. There are several initiatives at the Agency to modify USPI structure and content. Should Immunex Corporation plan to submit the USPI using current standards or will the new Physician Labeling Rule and/or the SPL structure be in use at that time (Section 4.5.2)?*

FDA Faxed Response:

Structured product labeling will go into effect fall 2005. Once-SPL is in effect, the procedures for submitting SPL should be followed. If the Physician Labeling Rule goes into effect, those rules will apply as well.

Further Discussion:

Amgen agreed to FDA's comments, and would submit the appropriate labeling based upon those rules that were in effect at the time of submission.

16. *Does the Agency have any additional questions concerning the content and presentation of data in the license application that may be addressed at or following the Type C meeting?*

FDA Faxed Response:

Please see below.

Additional Faxed Comments/Recommendations:

PRECLINICAL

1. Please provide complete study reports for all nonclinical pharmacology studies conducted with Panitumumab, including both *in vitro* evaluations, and *in vivo*, anti-tumor efficacy studies in the BLA submission. Please also include tabular summaries of the tumor volumes, body weights, and any available data for serum levels of Panitumumab for the individual animals in each treatment group, for each of the respective study reports.

Further Discussion:

Amgen agreed to provide the information.

2. Please include complete descriptions and characterization of the assay methodology used to measure the serum levels of Panitumumab, as well as the assay methodology used to detect the immunogenicity of Panitumumab as part of the final reports for all nonclinical pharmacokinetic and toxicology studies, as appropriate.

Further Discussion:

Amgen agreed to provide the information.

3. Please also provide data in the BLA submission that demonstrate that your assay for immunogenicity of Panitumumab can detect antibody against the product with serum levels of Panitumumab still present. If the assay is unable to detect immunogenicity of Panitumumab while the drug is still present, this will confound interpretation of any findings in the 13-week and 26-week toxicology studies.

Further Discussion:

Amgen clarified that they are using an ELISA to test monkey anti-human antibody (MAHA) responses, and that the data would be provided in the final study report. FDA stated that this appears to be acceptable but they would need to review the data prior to final concurrence.

CLINICAL PHARMACOLOGY and TOXICOLOGY

4. Please examine the extent of the effect that EGFr expression has on the pharmacokinetics of Panitumumab.

Further Discussion:

Amgen explained that they would examine EGFr expression as a covariate of the PK studies.

CLINICAL

5. Please include financial disclosure information of the individuals conducting the blinded central review of disease assessment, which is the primary dataset used to determine the endpoint of progression-free survival.

Further Discussion:

Amgen agreed to provide the information.

6. The case report forms generated by the blinded central review of disease assessment committee and any radiographs, as specifically identified by FDA during BLA review, that serve as primary records underlying FDA review and decisions will need to be officially submitted to the BLA. For any radiographic image information, which is provided for auditing purposes and is not considered primary data for decisional

IND 8382 5-24-05 Clinical/Preclinical MTG

purposes, please clarify whether the radiographic image information will be archived, and if so, describe the process for archival storage.

Further Discussion:

Amgen stated that they would provide the CRFs. Amgen agreed to discuss the issue of archiving those radiographs that would be necessary for FDA review and would be part of the BLA archival file at the telecon in which they discuss the requirements for radiologic imaging.

Action Items:

1. FDA agreed to review the fax submitted to FDA on March 17, 2005 and respond to Amgen via facsimile.
[please see attached addendum]
2. Amgen agreed to provide an integrated statistical analysis plan to FDA.
3. Amgen agreed to provide the slides that they had presented to FDA at the meeting as an amendment to their IND 8382.
4. FDA acknowledged Amgen's plan to apply for accelerated approval based on a progression free survival data and to submit a supplement for regular approval with disease free survival as the endpoint.
5. Amgen agreed to provide the 120 day safety update.
6. Amgen will proceed to set up a telecon with — to determine the requirements for submitting and archiving radiographic information.
7. FDA and Amgen agreed to further discussion regarding the 9 month toxicology studies and FDA agreed to consider further Amgen's proposal to accept the class labeling without the 9 month studies.
8. Amgen agreed to submit the final study report for the 6 month toxicology study.
9. Amgen agreed to submit the formal request for pediatric deferral and the proposal for pediatric studies.

10.

12 - IND 8382 5-24-05 Clinical/Preclinical MTG

11. Amgen will provide the integrated immunogenicity report and will follow up with FDA regarding a telecon.
12. Amgen will provide a backup plan for a confirmatory trial in the event that 20020408 does not meet the accelerated approval study endpoints.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

FDA Attendees:

Center for Drug Evaluation and Research

Shana Fuchs, Ph.D.
Ruthann Giusti, M.D.
Joseph Gootenberg, M.D.
Monica Hughes, M.S.
Karen Jones
Hsien Wu Ju, M.D.
Patricia Keegan, M.D.
Kallappa Koti, Ph.D.
Lydia Martynec, M.D.
Anne Pilaro, Ph.D.
David Ross, M.D.
Mark Rothmann, Ph.D.
Dale Slavin, Ph.D.
Patrick Swann, Ph.D.
Karen Weiss, M.D.
Hong Zhao, Ph.D.

Center for Devices and Radiological Health

Robert Becker, M.D.

Sponsor Attendees:

Amgen/Immunex/Abgenix

Janice Castillo, B.S.
Alessandra Cesano, M.D.
Julie Lepin, B.S.
Barbara Mounho, Ph.D., DBAT
Matthew J. Neal, M.A.
Linda J. Paradiso, D.V.M., M.B.A.
Gisela Schwab, M.D.
Mary Celine Scott, Ph.D., M.B.A.
Sophie Visonneau, Ph.D.
Michael Wolf, M.S.
Bing-Bing Yang, Ph.D.

V.P., Regulatory Affairs Abgenix
Sr. Director, Oncology Therapeutic Area
Sr. Mgr, Regulatory Affairs
Principal Sci., Toxicology
Mgr, Regulatory Affairs
Sr. Dir., Oncology Regulatory Affairs
Chief Medical Officer Abgenix
Sr. Mgr., Regulatory Affairs
Assoc. Dir., Oncology Therapeutic Area
Assoc. Dir., Biostatistics
Assoc. Dir, Pharmacokinetics

MEETING ATTENDANCE LIST

between Amgen and
 Center for Drug Evaluation and Research.

DATE: 5-24-05 TIME: 3³⁰ - 5⁰⁰ pm ROOM: WCC 2 G

NAME - Please print	AFFILIATION
Dale C. Slavin	CDER
Karen Weiss	CDER
Patricia Keegan	CDER
ALESSANDRA CESANO	AMGEN
SOPHIE VISONNEAU	AMGEN
BING - BING YANG	AMGEN
Barbara Mounko	Amgen
JANICE CASTILLO	ABGENIX
GISELA SCHWAB	ABGENIX
Linda J. Paradise	Amgen
Julie Lepin	Amgen.
Michael Wolf	Amgen
Mary Celine Scott	AMGEN
MATTHEW J. NEAL	AMGEN
PATRICK SWANN	CDER
Joe Goodenberg	CDER
Ruthann Gust	CDER
H. W. Ju	CDER
Chara Fuchs	CDER
Anne Pilaro	CDER
Robert Becker	CDRH/OIND
Karen Jones	CDER/ODE 6
David Ross	ODE 6
Monica Hughes	CDER/ODE-6
LYDIA MARTYNEC	CDER/ODE-6
Hong Zhao	CDER/ODE-6
Kallappa KOTI	CDER/OB

Food and Drug Administration
Rockville, MD 20852

Our Reference: BB-IND 8382

JUN 21 2005

Amgen, Incorporated
Attention: Mary Celine Scott, Ph.D., M.B.A.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Scott:

Please refer to your **Investigational New Drug Application (IND)** for "Panitumumab [Human Monoclonal Antibody (ABX-EGF)(Abgenix) to Epidermal Growth Factor Receptor]" and to the meeting held on May 26, 2005, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,



Dale Slavin, Ph.D.
Regulatory Project Manager
Division of Review Management, and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

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10 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

JUN 23 2005

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: June 7, 2005
From: Ruthann Giusti, M.D. through Dale Slavin, Ph.D., RPM 
ODEVI/DTBOP/DRMP
Subject: Revised Facsimile to Amgen re 5-24-05 Type C meeting (Amgen revisions submitted via 5-17-05 fax)
To: IND 8382

FDA has the following revised responses to your update to the meeting materials faxed on May 17, 2005 prior to the Type C Meeting held on May 24, 2005:

1. **EGFr Inhibitor-related Events Tegument Related-toxicity Terms**

Skin toxicities/disorders, Nail disorders, Hair disorders, Eye disorders, Chelitis
Two Analyses:

- 3-step approach
 1. MedDRA Version 8.0 terms will be identified programmatically in Study 20020408
 2. Specific terms with a 5% or higher difference in incidence between Panitumumab and BSC arms will be identified
 3. These specific terms will be used to scan pooled database in CSS
- Pre-specified terms agreed with the FDA during the review of the Cetuximab license application (see FDA SBA) for Skin Toxicities
 - acneform rash, acne, maculopapular rash, pustular rash, rash, exfoliative dermatitis, dry skin

FDA RESPONSE:

This proposal is acceptable.

2. Provision of CRFs : Modified Proposal

- Submission of ALL CRFs for Panitumumab monotherapy studies conducted in/including mCRC subjects, and/or supportive of PK and/or target indication
 - 20020408, 20030167, 20030250, 20025405, 20030194, 20030251, 20030138, 20040116, 20020375
- NO submission of CRFs for monotherapy studies conducted in subject population(s) different from the one in Target indication
 - 20030110, 20020374, 20025408
- NO submission of CRFs for studies of Panitumumab in combination with chemotherapy
 - 2002504 part 1 and part 2, 20025409 part 1 and part 2
- NO submission of CRFs for study of Panitumumab monotherapy in Japanese subjects (same proposal)
 - 20040192

FDA RESPONSE:

This approach is acceptable provided that you confirm that you will submit, for all protocols, the following information:

1. Copies of written safety reports submitted to your IND for all patients with serious adverse drug experiences [as per 21 CFR 312.32].
2. CRFs for all patients who died on study or withdrew from study due to an adverse event [as per 21 CFR 314.50 (f)(2)].

**APPEARS THIS WAY
ON ORIGINAL**

IND 8382 revised Facsimile re: 5-17-05 fax

Updated Clinical Data Cut-off Dates

Study Number	Data Cutoff Date	At time of Data Cut - Off			Estimated Maximum Months of Exposure*
		Accrual Status	Subjects Treated	Subjects with Treatment Ongoing ¹	
20020408	30-Jun-05	Closed	~231 (436 in both arms)	~26 (31 in both arms)	~16
20025409 Part 2	02-Feb-05	Closed	24	2	~21
20030167	20-May-05	Open	93	~37	~17
20030194	30-Jun-05	Open	~188	~70	~14
20030251	13-May-05	Open	57	~18	~9
20040116	25-Aug-04	Closed	20	2	~5
20040192	16-May-05	Open	~12	~5	~4

* from First Dose to the Time of the LA Submission For Subjects With Treatment Ongoing

FDA RESPONSE:

This proposal is acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

Food and Drug Administration
Rockville, MD 20852

DEC 30 2004

Our Reference: BB-IND 8382

Amgen, Incorporated
Attention: Mary Celine Scott, Ph.D., M.B.A.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Scott:

Please refer to your **Investigational New Drug Application (IND)** for "Panitumumab [Human Monoclonal Antibody (ABX-EGF)(Abgenix) to Epidermal Growth Factor Receptor] ... and to the telephone conversation held on December 6, 2004, between representatives of your firm and this agency. A copy of our memorandum of that telephone conversation is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,



Dale Slavin, Ph.D.
Regulatory Project Manager
Division of Review Management, and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

CONCURRENCE PAGE



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: DEC 30 2004
From: Dale Slavin, Ph.D., ODEVI/DTBOP/DRMP *DS*
To: IND 8382
Subject: Type C Meeting Summary

Teleconference Date: December 6, 2004 Time: 11:00 am to 12:00 pm

Location: Woodmont Office Complex 2 6th Floor Conference Room G

Meeting Requestor/Sponsor: Amgen Inc.

Product: *Panitumumab [Human Monoclonal Antibody (ABX-EGF)(Abgenix) to Epidermal Growth Factor Receptor]*

Proposed Use:

Type of meeting: Type C

Meeting Purpose: To discuss the status of 4 clinical trials (20025405, 20030167, 20030250 & 20020408), the use of improvement in progression free survival as an acceptable endpoint for regular approval and to discuss the above issues in the context of an indication and a future BLA submission

FDA faxed draft comments to Amgen on December 3, 2004. Amgen requested that questions 2, 5 and 7, be discussed in further detail.

Sponsor questions and FDA response:

Study 20030167 is a phase 2 single-arm study of panitumumab for 3rd/4th-line treatment of patients with metastatic CRC who developed progressive disease or relapsed while on or after prior chemotherapy. This study was intended to serve as the basis of accelerated approval for panitumumab using a study designed with input from the Division via the SPA process. In light of significant enrollment challenges to Study 20030167 which have intensified

following the approvals of cetuximab and bevacizumab, Immunex proposes that Study 20020408, a phase 3 randomized controlled trial comparing best supportive care (BSC) alone to BSC plus panitumumab in 3rd/4th-line treatment of patients with metastatic CRC who developed progressive disease or relapsed while on or after prior chemotherapy, serve as the pivotal study in a BLA for panitumumab. With the exception of the EGFr expression inclusion criterion, the patient population enrolled into Study 20020408 mirrors that agreed upon with the Agency under the SPA for Study 20030167. In addition charters (i.e., independent central review to determine eligibility and on-study, independent data monitoring committee) and case report forms similar to those developed for Study 20030167 and agreed upon with the Agency under the SPA have been put in place for Study 20020408. Additionally, Study 20025405, a phase 2, multi-center, open-label single-arm study of panitumumab as treatment for patients with metastatic CRC who failed prior chemotherapy is near completion, with only one subject remaining, and will complete at the time of filing.

1. *Does the Agency concur that Study 20020408 may serve as the pivotal proof of efficacy trial for approval of panitumumab _____ with supporting data from Study 20025405 plus available data from Study 20030167?*

FDA Faxed Response:

Yes, the proposed pivotal (20020408) and supporting studies for colorectal cancer (20025405, 20030167), and other supporting studies would be acceptable for filing.

2. *Based on recent ODAC presentations and discussions (November 2003, May 2004), Immunex has inferred that a significantly robust and durable improvement in PFS in first-line CRC may constitute clinical benefit and serve as the basis for regular "full" approval. If study results from the randomized, controlled multi-center Study 20020408, were to provide evidence of robust and durable efficacy in 3rd/4th-line CRC, could this study, in combination with supportive data from other studies described for this program support regular "full" approval of panitumumab _____*

FDA Faxed Response:

Yes, a significantly robust and durable improvement in PFS found in the pivotal study could support approval of Panitumumab _____

Survival data should be submitted to determine the type of approval.

Further Discussion:

FDA clarified that if the primary endpoint of progression free survival (PFS) is found at the time of filing to be robust and durable, then accelerated approval is an option. A significant advantage in overall survival (OS) could lead to regular approval.

A number of existing aspects and proposed changes to the statistical analysis plan for Study 20020408 are identified in Section 5.2.2 for which Agency advice is requested.

- *Immunex intends to change the primary efficacy analysis population from the Adjudicated Prior Failures analysis set to the Intention-to-Treat analysis (ITT) set. The Adjudicated Prior Failures analysis would be retained as a secondary analysis set.*

FDA Faxed Response:

The change in the analysis set for the primary efficacy analyses is acceptable. The adjudicated prior failure analysis set may be used as secondary analyses for the primary and secondary efficacy endpoints.

In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints cannot result in (either singly or in combination) an efficacy claim. In the presence of a statistically significant result for the primary analysis of the primary endpoint, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future revised protocol, how adjustments will be made for multiplicity to guarantee an overall 0.05 level for secondary endpoints.

- *Protocol Amendment #2 expanded the EGFr testing inclusion criteria from $\geq 10\%$ EGFr expression by central laboratory assessment to $\geq 1\%$ EGFr expression by central laboratory assessment. It is our intent to include all randomized subjects, regardless of EGFr expression, in the ITT primary efficacy analyses.*

FDA Faxed Response:

These changes are acceptable.

- *The primary statistical analysis plan is to compare progression-free survival (PFS) by a stratified log-rank test with 3 factors. Two of these factors were used to stratify randomization, ECOG performance status (0-1 vs 2), and region (Western Europe vs Central and Eastern Europe vs rest-of-world). The third factor is EGFr expression categorized as 1% to 9% vs $\geq 10\%$.*

FDA Faxed Response:

The primary analysis for PFS should be based on a stratified log-rank test stratified by the 2 factors used in randomization, i.e., ECOG performance status (0-1 vs 2), and region (Western Europe vs Central and Eastern Europe vs rest-of-world). The stratified log-rank test with 3 factors may be used as an exploratory analysis for the PFS.

- *Objective tumor response will be determined based on modified-RECIST criteria both by the local investigator and through central review of the imaging scans. The original plan was to perform the primary efficacy analyses of PFS based on the central review. However, the investigator will make treatment decisions based on local review of scans which may not be in concordance with central review, thus potentially skewing the PFS endpoint. Because of this, we propose basing the primary analyses on the local review, and to include exploratory analyses of outcome assessments (objective responses and PFS) per central review, and local-central concordance.*

FDA Faxed Response:

No, since it is important to evaluate the objective responses and PFS in a consistent manner, results based on central review should be used for the outcome assessments. Please include sensitivity analyses based on local review or a combination of local and central reviews.

- *Revised language in the statistical considerations Section is proposed to clarify (1) the hypothesized treatment effect, (2) the target number of events (progression or death) required for the primary analysis, and (3) the sample size utilizing an ITT rather than an Adjudicated Prior Failures analysis set in the primary analysis.*

FDA Faxed Response:

These changes are acceptable.

3. *Does the Agency agree with the proposed changes in the Study 20020408 Statistical Analysis Plan?*

FDA Faxed Response:

Yes. However, a detailed statistical analysis plan for study 20020408 should be submitted.

4. *If the study meets the protocol-specified criteria for efficacy, and panitumumab has an acceptable safety profile, does the Agency agree that these data could be the primary clinical data supporting marketing approval?*

FDA Faxed Response:

Yes, these data could support filing.

5. *Study 20020408 includes patients with low (1% to 9%) EGFr staining intensity. The statistical plan in Section 5.2.2 describes proposed analyses of this subset, which will examine the relative treatment effect on PFS by EGFr status and objective response within the active arm. Study 20030250, a Phase 2 single-arm study of panitumumab*

for 3rd/4th-line treatment of patients with metastatic CRC who developed progressive disease or relapsed while on or after prior chemotherapy, mirrors Study 20030167 with the exception that it will be conducted in subjects with 0% to 9% EGFr expression. Similarly charters and case report forms have been put in place for this study in agreement with those developed for Study 20030167. This study will not be completed by the time of our BLA filing, but an unplanned interim analysis of this study will be conducted and included in the dossier.

FDA Faxed Response:

Since an EGFr detection assay kit was used to characterize the study population, information about the assay would need to be included in the label.

Further Discussion:

At the time of submission, over 1000 subjects (Table 7-1) with solid tumors will have been treated with panitumumab at dosages ranging from 0.01 mg/kg to 5 mg/kg once weekly, 6.0 mg/kg once every 2 weeks, and 9.0 mg/kg once every 3 weeks; the data set will include approximately 500 subjects treated at 2.5 mg/kg once weekly and approximately 500 subjects treated with 6.0 mg/kg once every 2 weeks (Table 7-4).

6. *Does the Agency agree that the combined safety data at the time of submission is adequate?*

FDA Faxed Response:

Yes, the combined safety data is acceptable for filing.

7.

In preparation for commercialization, the site and scale of panitumumab manufacturing have been modified. As outlined in Section 7.2, Study 20030251 was designed to test the hypothesis that material produced at the — scale would have an acceptable toxicity profile and would achieve the expected drug exposure when administered as 6 mg/kg once every 2 weeks and 9 mg/kg once every 3 weeks. Data will be compared to those obtained from Study 20030138, which was conducted with material manufactured at the — scale.

8. *Does the Agency agree that this characterization is adequate to support commercialization of panitumumab manufactured at the — scale?*

FDA Faxed Response:

See the answer to the previous question regarding the —
The PK comparability between — CHO material and — CHO material will be evaluated through a cross-study comparison (Study 20030138 used — CHO material and Study 20030251 will use — CHO material). This approach is acceptable since the manufacturing change is a scale-up and the apparent comparability between these two materials has been demonstrated in cynomolgus monkeys (Study 103917) after the first dose. From the information submitted, thus far, the products appear to have comparable biochemical profiles. Likewise, the pharm tox information submitted thus far appears to be adequate. The results of Study 20030251 along with the information from other clinical studies using the 6 mg/kg q 2 week dosing schedule would appear to be adequate to support the 6 mg/kg q 2 week dosing schedule.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

FDA Attendees:

Center for Drug Evaluation and Review

DTBOP

Ruthann Giusti, M.D.

Robert Justice, M.D.

Dale Slavin, Ph.D

Hong Zhao, Ph.D.

OB

Mark Rothmann, Ph.D.

Yuan Li Shen, Dr. P.H.

Sponsor Attendees:

Amgen, Inc.

Alessandra Cesano, MD

Steve Dahlberg, MS

Linda J. Paradiso, DVM, MBA

David R. Parkinson, MD

Mary Celine Scott, PhD, MBA

Sophie Visonneau, PhD

Michael Wolf, MS

Bing-Bing Yang, PhD

Dir., Global Development, Oncology

Dir., Biostatistics - Oncology

Sr. Dir, Regulatory Affairs, Oncology

V.P., Global Development, Oncology

Sr. Mgr., Regulatory Affairs

Assoc. Dir., Oncology Therapeutic Area

Assoc. Dir, Biostatistics

Assoc. Dir., Pharmacokinetics & Drug Metabolism

Abgenix

Janice Castillo, BS

V.P., Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

Food and Drug Administration
Rockville, MD 20852

Our Reference: BB-IND 8382

Immunex Corporation
Attention: Douglas Hunt
Director, Regulatory Affairs
One Amgen Center
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Please refer to your **Investigational New Drug Application (IND)** for "Human Monoclonal Antibody (ABX-EGF) (Abgenix) to the Epidermal Growth Factor Receptor" and to the meeting held on June 19, 2003, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,



Sharon Sickafuse
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Office of New Drugs
Center for Drugs
Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: July 18, 2003 **SKS**
From: Sharon Sickafuse, CDER/ODE6/OTRR/DARP
To: IND 8382
Subject: CMC PrePhase 3 Type B Meeting Summary

Meeting Date: June 19, 2003

Meeting Requestor: Immunex/Amgen

Product: Human Monoclonal Antibody (ABX-EGF) (Abgenix) to the Epidermal Growth Factor Receptor

Proposed Use:

Type of meeting: CMC prePhase 3

Meeting Purpose: Discuss plans for CHO production process and scale-up

Sponsor questions and FDA response:

1. *Is the proposed plan for evaluating comparability of ABX-EGF produced from the — hybridoma — process to the — CHO Immunex process acceptable to the Agency?*

The proposed plan, comparing biochemical properties and *in vitro* potency of ABX-EGF from the hybridoma and CHO processes appears acceptable for this phase of clinical development with the changes listed below and in conjunction with the animal PK data.

FDA recommends that the following modifications be incorporated into Immunex's plan for biochemical comparison of the — CHO process to the — hybridoma process:

- Acceptance Criteria for the Immunex-developed assays should be based on data generated from the hybridoma lots analyzed using the Immunex assays. Based on section 7.2 of the May 20, 2003, submission, Immunex's plan is for showing

consistency between the CHO development lots and CHO clinical lots rather than comparability of CHO-derived ABX-EGF to hybridoma-derived ABX-EGF.

- For assays in which clear differences exist between hybridoma and CHO-derived ABX-EGF (e.g. $r = \text{---}$), please identify the cause for this difference and assess the potential affect on potency, immunogenicity and product stability.
 - Please set Acceptance Criteria for potency assays --- based on previous hybridoma-derived ABX-EGF lot release data.
 - Please include accelerated stability data for the clinical lots in the protocol comparing CHO-derived to hybridoma-derived ABX-EGF. Accelerated stability studies for this purpose should be conducted side-by-side with representative lots of the hybridoma material.
 - Please include a test which compares --- Alternatively, please submit data to support that the CHO-derived and hybridoma-derived ABX-EGF ---
 - There are 2 reference standards identified in the May 20, 2003 submission: the current reference standard, hybridoma lot 4645, and CHO lot 1504-04. Please identify the reference standard used for comparability, especially in those assays for which the acceptance criteria contain "comparable to reference".
 - When submitting results of the biochemical comparability testing, the data submitted should include results from the --- hybridoma lots described --- (lots + reference standard lot) and the --- CHO lots --- (GMP lots + reference standard lot) for all assays.
 - Please submit mass spectrometry data on representative lots.
 - Please include information from --- validation, and country of origin for any animal-derived components. These data, as well as any animal pharm/tox data will need to be reviewed by the FDA prior to using the CHO-derived material in clinical trials.
 - Cell line stability data will need to be part of the BLA.
2. *Are the proposed lot release specifications acceptable?*
- In order to appropriately assess the specifications, please submit a table of the hybridoma-derived ABX-EGF drug substance and drug product testing/release

data. For assay methods developed at Immunex, please include the lots of hybridoma material tested using the Immunex analytical methods.

- Based on data in the May 20, 2003, submission for (lots of ABX-EGF (lots of hybridoma product and lots of CHO product), FDA recommends tightening the reduced specifications.
- FDA recommends that the assay acceptance criteria be set based on the hybridoma lot release experience.
- FDA recommends that the assay be reinstated. Once Immunex has collected data on this assay using the CHO-derived material and can demonstrate that this assay is no longer necessary, it can be dropped.
- Please report lot release acceptance criteria as units/mg ABX-EGF rather than units/dose. For example, DNA acceptance criteria is listed as $\leq 10\text{ng/dose}$ (current lot release acceptance criteria for DNA is $\leq 2\text{pg/mg ABX-EGF}$).
- The endotoxin acceptance criteria is set at $\leq 1\text{EU/dose}$. This is at the maximal allowable limit for a 70 kg person, but may be too high for a late stage cancer patient who would weigh less. ABX-EGF used in clinical trials to date had a release specification of $\leq 0.5\text{EU/mg}$, a significantly lower level than that which Immunex has set for the CHO product. Immunex clarified that they have changed the endotoxin release specification for the CHO-derived product to $\leq 0.5\text{EU/mg}$. Immunex clarified that they have changed the endotoxin release specification for the CHO-derived product to $\leq 0.5\text{EU/mg}$.
- Please add the assay to the routine lot release assays while product manufacturing changes are planned. This will allow additional experience with the CHO product to enable setting appropriate acceptance criteria for future manufacturing changes.
- Immunex stated that ABX-EGF is filtered during infusion. Therefore, the USP assay for particulates is not included in the lot release specifications.
- FDA recommends that lot release specifications be re-assessed when sufficient lot experience has been accumulated for the CHO-derived product, and prior to submission of a BLA.

3. Please comment on the proposed plans for commercial production at

- Please submit a detailed comparability plan. For the comparability, tight acceptance criteria should be set based on the product data.
- Please identify the clinical trials in which the safety of the scale ABX-EGF will be assessed. Immunex stated that they will use the CHO-derived material in their pivotal studies. The confirmatory trial may use the material or the commercial material (), however, they will not mix material within the trial. Immunex plans to start their studies in September or October.

Additional FDA Comments and Questions:

- Please submit a detailed description of the immunogenicity and PK assays and identify any changes to these assays that were necessary due to the change from hybridoma to CHO production.
- Please identify the source of used for production of the CHO-derived ABX-EGF, as well as if any human or animal material was used in its purification.
- Please provide data supporting the statement on page 26 of the May 20, 2003, submission that there is no biological impact between. Are controlled for in the stability protocol?
- Please provide characterization data of the acidic isoforms for CHO-derived ABX-EGF.
- What is the sensitivity of the bioassay and assay to detect changes in the product?
- How does the assay compare with the assay? Please describe this assay.
- Because ABX-EGF is filtered during infusion, FDA recommends that stability studies be conducted to characterize the effect of this filtration on ABX-EGF.



Our Reference: BB-IND 8382

JUL 09 2003

Immunex Corporation
Attention: Douglas Hunt
Director, Regulatory Affairs
One Amgen Center
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Please refer to your **Investigational New Drug Application (IND)** for "Human Monoclonal Antibody (ABX-EGF) (Abgenix) to the Epidermal Growth Factor Receptor" and to the telephone conversation held on June 10, 2003, between representatives of your firm and this agency. A copy of our memorandum of that telephone conversation is attached for your information.

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,

Sharon Sickafuse

Sharon Sickafuse
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Office of New Drugs
Center for Drugs
Evaluation and Research

Enclosure: Teleconference Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: July 9, 2003

From: Sharon Sickafuse CDER/ODE6/OTRR/DARP

To: IND 8382

Subject: Type B Teleconference Summary

Teleconference Date: June 10, 2003

Sponsor: Immunex/Amgen

Product: Human Monoclonal Antibody (ABX-EGF) (Abgenix) to the Epidermal Growth Factor Receptor

Proposed Use:

Type of meeting: Clinical prePhase 3

Meeting Purpose: Discuss proposed Phase 3 trial, proposed Fast Track request, and registration strategy

Immunex proposed a registration strategy consisting of the following components:

1. ABX-EGF as monotherapy in colorectal cancer patients who have failed previous therapies. Study ABX-0305 is completed and is a single arm, Phase 2 study in 150 patients using hydridoma-derived material. Patients had to have failed 5-FU either with or without leucovorin and also failed either irinotecan, oxaliplatin or the combination of irinotecan and oxaliplatin to be eligible. A final study report for ABX-0305 will be submitted in approximately 6 months. A second Phase 2 single arm study using CHO cell-derived material is proposed. Patients will have to have failed 5-FU, leucovorin, irinotecan, and oxaliplatin to be eligible. Immunex plans to submit a BLA under Accelerated Approval using response rate data from these two studies.

2.

3. ABX-EGF plus best supportive care (BSC) versus BSC alone in patients who have failed previous chemotherapy (protocol 20020408). The primary endpoint of this European study would be time to progression. This study will use the CHO-cell derived material.

Sponsor questions and FDA response:

1. *Does the Agency consider colorectal cancer subjects who have failed 5-FU, leucovorin, irinotecan and oxaliplatin an appropriate population to study for Accelerated Approval?*

- Yes, this would be acceptable provided no additional agents are approved for the treatment of metastatic colorectal cancer prior to the review and approval of this license application. If additional agents are approved, this population would not be appropriate in support of accelerated approval. In this clinical setting, Immunex will be required to provide definitive evidence of clinical benefit for ABX-EGF in order to support approval (e.g., completion of the Phase 3 study with evidence of a robust statistical effect demonstrating improved survival as compared to best supportive care).
- Protocol 20020408 (see the May 9, 2003, submission for the proposed protocol) stratifies patients based on prior exposure to oxaliplatin stating that oxaliplatin is not available in some countries. Please identify the countries where oxaliplatin is not available. Please be aware that if oxaliplatin is granted standard approval based on confirmation of clinical benefit, the data obtained in patients who are not refractory to oxaliplatin could not be included in the primary efficacy database, but should be considered supportive data demonstrating activity.
- FDA asked for clarification of the plan to document refractoriness to 5-FU, leucovorin, irinotecan and oxaliplatin.

For study ABX-0305, Immunex was asked to provide examples of source documentation used to determine refractoriness of patients to chemotherapy. For the new proposed single arm Phase 2 study, which will use the CHO-derived material, Immunex stated that they will use an Independent Response Committee (IRC) to confirm refractoriness. FDA asked Immunex to submit the IRC charter including information on the criteria used to determine refractoriness and how the source documents will be archived at the clinical sites.

2. *Does the Agency consider that the combined data from the two, Phase 2 single arm studies in this patient population would represent an acceptable approach to support a license application under Accelerated Approval?*
- Immunex proposes to use the data from ABX-0305 and initiate a second single arm study to reach an N ~ 300 to support approval. FDA cannot address this question at this time because it is unclear what Immunex means by the term “combined efficacy data” and the proposed second single arm Phase 2 study protocol has not been submitted in sufficient time for review.
 - The study design for Protocol 20020408, with modifications, would be of adequate design for accelerated approval, provided that no additional products are granted standard approval for the treatment of metastatic colorectal cancer in the interim.
 - Accelerated approval may be granted based on demonstration of a medically important and durable objective response rate or improved time to progression (progression-free survival) if adequate data are available, even if another product has received accelerated approval for the same indication. For a biologic product, where objective tumor responses have not always correlated with improved overall survival, FDA believes that a time to event endpoint (e.g., time-to-progression or progression-free survival) would be a better choice as a surrogate endpoint for accelerated approval.
 - For a study to be considered adequate to support accelerated approval the following conditions must be met:
 - The protocol has been reviewed and found acceptable for use as a major efficacy trial to support accelerated approval. FDA recommends submission of the 3 proposed protocols as requests for Special Protocol Assessment (SPA). The package for such a request should include:
 1. A detailed protocol
 2. The entire CRF used to collect data for study enrollees
 3. Detailed statistical analytical plan
 4. Final Data Safety Monitoring Board (DSMB) Charter
 5. Final Independent Radiological Review (IRR) Charter including a table of the RECIST criteria, Immunex’s proposed modifications to these criteria, and the rationale for the modification.
 6. Final Oncology Response Review (ORR) Charter, if applicable
 7. Questions about the study design, adequacy of data collection, statistical plan, case report forms, DSMB charter, IRR charter, and CRF

Depending upon the design (particularly the power) of the proposed Phase 4 study, additional studies may be required for full approval.

- The population studied must support the proposed indication. The refractoriness of patients to irinotecan and oxaliplatin as well as 5-FU and leucovorin must be clearly documented with radiologic studies in addition to clinical data on all patients enrolled on both studies. Such documentation will be required in support of a license application for accelerated approval.
- The toxicity profile must be clearly defined and adequate information available to assess toxicities related to experimental therapy for both studies. The supporting safety database must be adequate. Immunex stated that for study ABX-0305, all adverse events that occurred up to 30 days after ABX-EGF administration were captured. Patients with adverse events were followed until resolution for up to 2 years. FDA stated that this was acceptable.
- The size of the database must be adequate to demonstrate an objective durable response rate, improved time to progression or improved progression free survival with reasonable precision. There must also be adequate assessment of the toxicity profile ($N \geq 300$ receiving ABX-EGF). The product that was used in the trials must be demonstrated to be comparable to the product that is licensed.

3. *Does the Agency agree that the use of ABX-EGF in this CRC population would qualify for Fast Track designation?*

FDA recommended that Immunex submit a package requesting Fast Track Designation. The package should include a detailed summary of all information about the entire drug development plan including the study design for all proposed studies that would be used to support accelerated and full approval of the product in the desired indication. FDA can make no assessment about Fast Track Designation prior to review of the package and determination of its adequacy. Full (standard) Approval of another product for the same indication in the same population may result in withdrawal of the fast track designation if the new product addresses the unmet medical need for which ABX-EGF is being proposed.

4. *It is likely that there will be a significant number of investigational sites outside of the United States, including Western, Central, and Eastern Europe; Australia; and Canada, under BB-IND 8382 and in accordance with Good Clinical Practice (GCP). Does the Agency agree that these data can be used as support towards full approval in the USA?*

Data from foreign sites may be used to support full (standard) and accelerated approval. However, Immunex is responsible for ensuring that the conduct of any clinical trial at

any site conforms with GCP guidelines. Immunex or their subcontractor is responsible for ensuring that all pertinent data related to the study is collected at all study sites where patients are enrolled. The imaging data from all sites should be comparable with regard to technique and quality.

5. *Does the Agency agree that the proposed safety database including the 2 single arm trials (> 300) and a total safety database across all studies and indications estimated at over 1000 subjects will be adequate to support Accelerated Approval?*

Before FDA can make an assessment of acceptability, FDA will need the following information

- The type of the data collected for each study.
- The duration of data collection for each study.
- Auditing plan for all studies to ensure accuracy of safety data.
- The nomenclature used to classify the adverse events.
- The toxicity criteria used to assess toxicity for each study (e.g., NCI-CTC version 2.0. It is acceptable to use NCI-CTC version 3.0, but all studies should use the same version of the NCI-CTC).
- The format in which the data will be submitted, for example, per trial or as an integrated summary of safety.

- 6a. *A validated diagnostic immunohistochemistry kit for the determination of EGFR expression will be used for subject selection in the pivotal study. Immunex proposes to evaluate the relationship between EGFR expression and response to ABX-EGF treatment*
Does the Agency have comments on this approach?

In order to address this question, Immunex needs submit the following information:

- The number of colorectal samples that were assessed for EGFR positivity using the Ventana Kit and using the DAKO kit. Immunex stated that 340 colorectal samples, 48 non-small cell lung cancer samples, and 64 renal cancer samples were assessed using the DAKO kit.
- Clarify which kit is proposed for use in the licensure trials. Immunex said that they compared 70 colorectal samples using the two different antibodies in the 2 kits and determined that the DAKO kit is more sensitive. Therefore, they have decided to use the DAKO kit.
-
- Clarify which kit(s) have been used to identify the patients in the Phase 2 studies. If more than one kit was used, please specify the number of patients

assessed with each kit. Please confirm that histopathologic slides are available for each patient enrolled in each of the Phase 2 studies for possible re-testing and performance of concordance testing between the test kit used in the clinical studies and newer kits/modifications of the kit that would be used as an adjunct to licensure. Immunex agreed to provide this information.

6b. *How does the Agency approach inclusion of diagnostic kit information in the Physician Information?*

The performance characteristics and a brief description of the assay used in patient selection would ordinarily be described in the package insert for ABX-EGF.

7. *Based on MUGA scan data in 185 subjects, no significant impact on ejection fraction has been associated with ABX-EGF. Immunex proposes to reduce the frequency of routine MUGA scans to baseline and follow-up after the last dose. Does the Agency agree this is acceptable?*

FDA can make no comments about rescinding the requirement for frequent MUGA scans until we have reviewed the ejection fraction (EF) data collected thus far. Please provide the following data for review as soon as possible:

- The EF for each patient at each time point that the patient was studied. Please provide in the tabular form for each study the following information: the patient identifier, the patient's disease, any prior chemotherapies, any prior cardiotoxic chemotherapies, any prior chest radiation, any history of a cardiac disease, history of and type of cardiac disease/hypertension, subject age, the enrollee's baseline EF (along with the institutional lower limit of normal for EF; i.e., patients may have had MUGAs done at more than one institution with different lower limits of normal), follow-up EF at each time point on study (along with information on whether the same site did the MUGA or the MUGA was performed at a different site, the institutional lower limit of normal for that site), and akinetic, hypokinetic and diskinetic wall motion.
- The following analyses for the entire data set as a SAS dataset:
 - For patients with normal baseline EF, the % (number) of patients who continued to have the same EF \pm 5% during study and the duration of follow-up.
 - The % in whom the EF appeared to improve overtime. Correlate the increase in ejection fraction with adverse events of diarrhea/dehydration.
 - The % (number) who had a decline in EF overtime analyzed by two month intervals. Include the total number at risk at each timepoint.

- o The % (number of patients) with normal or improved EF over time who had prior exposure to cardiotoxic chemo or biologic therapy. The % (number) with decreased EF who had prior exposure to cardiotoxic chemotherapy. Include information on the decline by two month intervals.
8. *Does the Agency agree that the proposed preclinical data (pharmacology and toxicology) to be presented in the license application (as described in the briefing document) are sufficient to support approval in a metastatic cancer population?*

FDA agrees that the proposed data are sufficient.

FDA Additional Comments Regarding Protocol 20020408:

- Please clearly define in the protocol the methods used to define refractoriness/resistance to all prior chemotherapies. The collection of data that document refractoriness must be described in the protocol and in accompanying case report forms.
- FDA recommended that time-to-progression (TTP) or progression-free survival (PFS) is a more appropriate surrogate endpoint than response rate. Immunex acknowledged this comment.
- Please discuss the post-progression use of monoclonal antibody therapy targeted to the EGFr in a subject on the BSC arm who has progressed. Will the study be adequately powered for survival if patients are crossed-over or receive another EGFr-targeted therapy? Immunex stated that they will collect survival data.
- Will the study be adequately powered to demonstrate improvement in TTP (disease-free survival) in the oxaliplatin-refractory/resistant population? For survival? Immunex did not provide a detailed response to these questions, however they will consider these issues in the design of the study.

Additional Discussion Regarding Study ABX-0305:

- Immunex clarified that regarding objective response, the best response at 8 weeks was captured. If a patient had a response at 8 weeks, the response was confirmed at 4 weeks.
- Regarding EGFr expression, Immunex clarified that all patients in the study had at least 10% of their cells stain 1, 2, or 3+.

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CONCURRENCE PAGE

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MEETING SUMMARY ENCLOSED (MS)

Concurrence box

Division	Name/Signature	Date
DARP	Sickafuse	7-9-03