

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125522Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: July 09, 2015
To: Administrative File, STN 125522/0
From: Lakshmi Rani Narasimhan, Ph.D., Reviewer, CDER/OPQ/OPF/DMA
Endorsement: Reyes Candau-Chacon, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: # 1080
Applicant: Amgen Inc.
Facility: Amgen Inc. (ATO), One Amgen Center Drive. Thousand Oaks, CA 91320 USA (FEI # 2026154) – Pre-filled syringe (PFS)
Amgen Manufacturing Ltd (AML), Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777 USA (FEI # 1000110364) - Pre-filled syringe (PFS) and Autoinjector (AI)/Pen
Product: Evolocumab (Repatha), AMG 145
Dosage: Sterile, preservative-free liquid formulation in a single-use PFS or AI/Pen for subcutaneous injection with a dose of 140mg/mL delivered in 1.0 mL.
Indication: For the treatment of adults with primary hyperlipidemia or mixed dyslipidemia and for the treatment of homozygous familial hypercholesterolemia (HoFH) in adults and adolescents aged 12 years and over.
Due Date: August 27, 2015.

Recommendation for Approvability: The drug product section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.

SUMMARY:

This addendum addresses the pending DMF (b) (4) review for the (b) (4). The (b) (4) information for the (b) (4) in the DMF was reviewed and found adequate. Refer to the DMF (b) (4) quality microbiology reviews #1 (June 16, 2015) and #1a (July 09, 2015).

Satisfactory

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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
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Date: June 16, 2015
To: Administrative File, STN 125522/0
From: Lakshmi Rani Narasimhan, Ph.D., Reviewer, CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: # 1080
Applicant: Amgen Inc.
Facility: Amgen Inc. (ATO), One Amgen Center Drive. Thousand Oaks, CA 91320 USA (FEI # 2026154) – Pre-filled syringe (PFS)
Amgen Manufacturing Ltd (AML), Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777 USA (FEI # 1000110364) - Pre-filled syringe (PFS) and Autoinjector (AI)/Pen
Product: Evolocumab (Repatha), AMG 145
Dosage: Sterile, preservative-free liquid formulation in a single-use PFS or AI/Pen for subcutaneous injection with a dose of 140mg/mL delivered in 1.0 mL.
Indication: For the treatment of adults with primary hyperlipidemia or mixed dyslipidemia and for the treatment of homozygous familial hypercholesterolemia (HoFH) in adults and adolescents aged 12 years and over.
Due Date: August 27, 2015.

Recommendation for Approvability: The drug product section of this BLA was reviewed from a product quality microbiology perspective. However, the DMF review for the (b) (4) (b) (4) is pending. The (b) (4) information in the DMF will be reviewed and completed in an addendum to this memo.

SUMMARY:
Amgen Inc. submitted a new biologics license application, STN 125522 to license evolocumab for the treatment of hyperlipidemia or mixed dyslipidemia and homozygous familial hypercholesterolemia (HoFH). Drug substance is manufactured by (b) (4), and drug product in pre-filled syringe is manufactured both at Amgen Inc., Thousand Oaks, CA (ATO), and Amgen Manufacturing Ltd. Juncos, Puerto Rico (AML) and the Autoinjector (AI)/Pen are manufactured at (AML).

The application was submitted in eCTD format and included Module 1.1.2-FDA form 356h, Module 1.2-Cover letter, and Module 2 and 3. Module 3 includes two drug product sections (3.2.P), one for each presentation (PFS and prefilled AI/pen), appendices (3.2.A.1, Facilities and Equipment and 3.2.A.2, Adventitious Agents Safety Evaluation), and a regional section (3.2.R). Letter of authorization (LOA) for Amgen’s Type V DMF 21000 to reference the information regarding (b) (4) processing operations at the AML site and a LOA for (b) (4) (b) (4) Type III DMF (b) (4) to review the (b) (4) Syringe System were provided.

INTRODUCTION

Evolocumab (AMG 145) is human monoclonal immunoglobulin G2 which has high affinity to human proprotein convertase subtilisin/kexin type 9 (PCSK9). It binds with high affinity to PCSK9 and inhibits the binding of PCSK9 to the low-density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The subsequent increase in LDLR results in decrease of low-density lipoprotein cholesterol (LDL-C) in serum. Evolocumab is a lipid-lowering therapy similar to statin and indicated for the treatment of adults with primary hyperlipidemia or mixed dyslipidemia and for the treatment of homozygous familial hypercholesterolemia (HoFH) in adults and adolescents aged 12 and above.

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

DRUG SUBSTANCE

Evolocumab is a human monoclonal antibody produced in Chinese hamster ovary (CHO) cells. The drug substance manufacturing process consists of (b) (4)

For the review of drug substance aspects of the application, please see review by Michael Shanks.

ASSESSMENTS**Drug Product Quality Microbiology Information Reviewed**

Sequence number	Date	Description
0008	October 23, 2014	Amendment
0018	January 08, 2015	Amendment
0023	February 18, 2015	Amendment
0031	March 06, 2015	Amendment
0040	April 09, 2015	Amendment
0047	May 08, 2015	Amendment
0052	May 22, 2015	Amendment
0064	June 10, 2015	Amendment

3.2.P. DRUG PRODUCT**Evolocumab -140mg/mL PFS**

The evolocumab drug product manufacturing process consists of (b) (4). Drug product is supplied in two presentations, prefilled syringe (PFS) and prefilled autoinjector/pen (AI/pen). Both presentations (b) (4) provide same dose of 140mg/mL. Drug product in PFS is filled at AML and ATO. AI/pen assembly is performed at AML.

3.2.P.1 Description and Composition of the Drug Product- Pre-Filled Syringe

Sterile, preservative-free solution of drug product is supplied in a prefilled syringe (PFS) for subcutaneous injection. The PFS contains 140 mg/mL evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0 in 1.0 mL (b) (4). The quantitative and qualitative composition of the drug product provided in Table 1 is duplicated below:

Table 1. Quantitative and Qualitative Composition of 140 mg/mL Prefilled Syringe

Component	Grade	Function	Concentration	Quantity (per dose)
Evolocumab	In house ^a	Active ingredient	140 mg/mL	140 mg
Proline	USP, PhEur, JP	(b) (4)	220 mM	25 mg
Acetic acid, glacial	USP, PhEur, JP	(b) (4)	20 mM	1.2 mg
Polysorbate 80	NF, PhEur, JP	(b) (4)	0.01% (w/v)	0.10 mg
Sodium hydroxide ^b	NF, PhEur, JP	(b) (4)	Titrate to pH 5.0	Titrate
Water for injection	USP, PhEur, JP	(b) (4)	(b) (4)	(b) (4)

^a Tested to internal specifications (3.2.S.4.1, Specification).

^b Sodium hydroxide may be used to adjust pH. The supplier tests sodium hydroxide (b) (4) to NF, PhEur, and JP standards.

3.2.P.2 Pharmaceutical Development

Process Development History

Type I glass vial used as the primary container in early phase clinical studies was changed to a Type I glass syringe in the late phase of clinical studies. This change also accompanied (b) (4) of the drug substance from 70 mg/mL to 140 mg/mL and a formulation change. Early and late phase clinical drug product was manufactured at ATO. (b) (4)

Commercial production of evolocumab drug product in PFS was validated (b) (4) at ATO and at AML (b) (4)

The manufacturing process flow and the container closure components used are the same at both sites.

Process Characterization

(b) (4)

Process Comparability ATO to AML (b) (4)

Process Comparison

The manufacturing process steps performed at both sites are the same with minor process variations which are reviewed in section 3.2.P.3.3.

Equipment Comparison

A comparison of the major equipment used at ATO and AML (b) (4) for the manufacture of 140 mg/mL PFS provided in Table 1 is reproduced below.

Table 1. Comparison of Major Equipment at Drug Product Manufacturing Sites

Processing Step	Site of Manufacturing	
	ATO	AML-1
(b) (4)		

Container Closure System

The prefilled syringe container closure system consists of a 1 mL Type I glass syringe with a staked-in-place stainless steel needle, (b) (4) needle shield (b) (4), and a (b) (4) plunger-stopper. The syringe barrel interior, needle outer surface, and the entire plunger-stopper are (b) (4). The (b) (4) needle shield is made from (b) (4) and may be supplemented with an outer plastic rigid needle shield cover. (b) (4). The (b) (4) syringes manufactured by (b) (4) are supplied (b) (4). The (b) (4) plunger-stoppers manufactured by (b) (4) are supplied (b) (4).

Reviewer's comments: Container closure components are received in a ready for use condition (b) (4)

Satisfactory

Container closure integrity:

Three CCI testing methods were qualified for the evolocumab glass syringe primary container system: 1) Microbial immersion, 2) Dye ingress, and 3) Vacuum decay.

Microbial immersion

(b) (4) syringes from each of the 3 media fill lots (Batch # 0010137666, 0010137668, and 0010137668) were used for CCI testing. Growth promotion testing was performed to ensure the viability of the culture media. (b) (4)

(b) (4)

The acceptance criteria for the test are (b) (4)

Results from the microbial immersion test showed no breach of CCI by demonstrating no growth. The following table providing the results is duplicated from the submission.

Table 1. Summary of Container Closure Integrity Testing via Microbial Immersion

Sample Set of Each Lot	Acceptance Criteria	Visual Inspection Results		
		Media batch 0010137666	Media batch 0010137668	Media batch 0010137669
10 Positive Control	(b) (4)	Pass ^a	Pass ^a	Pass ^a
(b) (4) Media Filled Syringes	(b) (4)	Pass ^b	Pass ^b	Pass ^b

a (b) (4)
b (b) (4)

FDA question (December 19, 2014):

- a. Please clarify and confirm if the PFS used for qualification of microbial immersion and dye ingress CCI test method are the same as the commercial PFS.
- b. Please submit the microbial immersion CCI test method qualification report for the evolocumab syringe primary container system. Report should include the following information: Description of the test including critical parameters (initial and final concentration of challenge organism, worst case pressure /vacuum challenge and time of exposure of sample units to the challenge), number of positive, negative controls and test units used in the study, preparation of positive and negative control and sensitivity of the method (LOD) as a function of breach size. In addition, describe how the final concentration of challenge organism was verified.

Firm's Response in amendment dated January 08, 2015 in sequence # 0018:

- a. Amgen confirmed that the PFS used for the qualification of microbial immersion, dye ingress and vacuum decay CCI test methods is the same as the commercial PFS.
- b. The microbial immersion CCI test method qualification report (RPT-001280, 01 Nov 2006) was provided in 3.2.R. (b) (4)

Reviewer's comments: The microbial immersion CCI test method was not qualified using worst case pressure or vacuum challenge. (b) (4)

FDA question (January 26, 2015):

- a. The microbial immersion CCI test method was not qualified using worst case pressure or vacuum challenge. (b) (4)

(b) (4)

CGMP Status

Please see Panorama

Conclusion

- I. The drug product section of this BLA was reviewed from a product quality microbiology perspective. However, the DMF review for the (b) (4) is pending. The DMF information will be reviewed and completed in an addendum to this memo.
- II. Product quality aspects other than microbiology should be reviewed by the OBP reviewer.
- III. The inspection of the drug product manufacturing site, AML (FEI #1000110364) was waived and ATO was inspected by the district from May 04-08 and 18-22, 2015.

Lakshmi
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CMC Microbiology Deficiencies for STN 125522/0 Evolocumab
Information Requests sent

15 October 2014

1. In Section 3.2.S.4.3 under *Bacterial Endotoxins*, you have stated that
 - a. Evolocumab drug product was tested for presence of pyrogens per USP <151>, Ph.Eur 2.6.8, and JP 4.04. Please move this information to the drug product section of the BLA and submit rabbit pyrogen test data for three different lots of the drug product to demonstrate that the drug product does not contain pyrogenic substances other than bacterial endotoxin.
 - b. [REDACTED] (b) (4)
Please submit the information and data from the endotoxin spiking study for the drug product with the protocol used to execute the study in the drug product section of the BLA.
2. Please clarify [REDACTED] (b) (4)
3. Please clarify [REDACTED] (b) (4)

December 12, 2014

I. Container closure integrity test

- a. Please clarify and confirm if the PFS used for qualification of microbial immersion, dye ingress and vacuum decay CCI test methods are the same as the commercial PFS.
Microbial immersion:
- b. Please submit the microbial immersion CCI test method qualification report for the evolocumab syringe primary container system. Report should include the following information: Description of the test including critical parameters (initial and final concentration of challenge organism, worst case pressure /vacuum challenge and time of exposure of sample units to the challenge), number of positive, negative controls and test units used in the study, preparation of positive and negative control and sensitivity of the method (LOD) as a function of breach size. In addition, describe how the final concentration of challenge organism was verified.
Dye Ingress:
- c. Please submit the dye ingress CCI test method qualification report for the evolocumab syringe primary container system with the following information : Description of the test including critical parameters (concentration of dye, worst case pressure /vacuum challenge and time of exposure of sample units to the challenge and dye), drug product lots used and number of positive, negative controls and test units used in the study, preparation of positive and negative controls, and sensitivity of the method (LOD) as a function of breach size. In addition, describe in detail how the LOD of the test was calculated.
- d. Please provide the correlation between the dye ingress test and microbial ingress test with respect to challenge conditions and breach size.
Vacuum Decay:
- e. Please provide rationale for including the vacuum decay method qualification in the BLA [REDACTED] (b) (4)



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

Date: June 2, 2015
To: Administrative File, STN 125522/0
From: Michael R. Shanks, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA
Subject: New Biologic License Application (BLA)
US License: 1080
Applicant: Amgen, Inc.
Mfg Facility: Drug Substance: [REDACTED] (b) (4)
[REDACTED])
Product: Repatha (evolocumab)
Dosage: Sterile, preservative-free liquid for subcutaneous injection, 140 mg/mL, in prefilled syringe (PFS) and autoinjector/pen (AI/Pen) presentations.
Indication: Treatment for the indications of (1) hyperlipidemia and mixed dyslipidemia & (2) homozygous familial hypercholesterolemia.
Due Date: August 27, 2015

Recommendation for Approvability: The drug substance section of this application, as amended, is recommended for approval from a microbiology product quality perspective.

Review summary

Amgen, Inc. has submitted this Biological License application (BLA) 125522 for evolocumab product approval. The drug substance (DS) is manufactured at [REDACTED] (b) (4)

BLA 125557 was submitted in eCTD on August 27, 2014. This review contains the assessment of evolocumab bulk drug substance section of the BLA 3.2.S. from a microbiological quality perspective. For review of drug product aspects of the application, please see review by Dr. Lakshmi Narasimhan.

The sponsor submitted the following amendments in response to requests for information:

Product Quality Microbiology Information Reviewed

Submission Type	Sequence Number	Sequence Date
Response to IR dated October 6, 2014 (request for manufacturing schedule)	0006	10/10/2014
Response to IR dated October 27, 2014 (Request to updated manufacturing schedule)	0011	11/03/2014
Response to IR dated December 19, 2014 (DS manufacturing microbial control deficiencies)	0021	01/12/2015
Response to IR dated January 23, 2015 (DS manufacturing microbial control deficiencies)	0022	01/29/2015
Response to IR dated March 16, 2015 (DS manufacturing inspectional deficiencies)	0034	04/02/2015

Assessment

3.2.S. Drug Substance (Substance – Manufacturer)

3.2.S.1 General Information

Evolocumab is a fully human monoclonal IgG2 that specifically binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9) and prevents its interaction with the low density lipoprotein receptor (LDLR). This in turn results in the lysosomal degradation of the LDLR rather than recycling of the LDLR to the cell membrane, thus increasing LDLR expression, and reducing serum LDL-C. Evolocumab is expressed as a secreted recombinant protein from Chinese hamster ovary (CHO) cells. (b) (4)

3.2.S.2. Manufacturing

3.2.S.2.1. Manufacturer(s)

The evolocumab drug substance manufacturing process consists of (b) (4). The following facilities listed in the BLA are used for the manufacture, release testing, and stability testing of evolocumab drug substance:

Manufacture, in-process, lot release and stability testing, and working cell bank storage of drug substance evolocumab are performed by (b) (4)

(b) (4)

Additional cell bank storage/production is performed by:

Amgen, Inc. (ATO)
One Amgen Center Drive
Thousand Oaks, CA 91320
FEI: 2026154

Amgen, Inc. Longmont Facility (ACO)
4000 Nelson Road
Longmont, CO 80503
FEI: 3002892484

Drug substance lot release and stability testing of evolocumab drug substance are performed at:

Amgen Manufacturing Ltd (AML)
Road 31, Kilometer 24.6
Juncos, Puerto Rico 00777
FEI: 1000110364

Drug substance (b) (4) ***viral testing are performed at:***

(b) (4)

Review comment: (b) (4) *was inspected on* (b) (4) *by a team of investigators led by Dr. Steven Fong under FACTS assignment* (b) (4) *A one item Form FDA 483 was issued with an initial recommendation of VAI. The compliance statuses of all facilities associated with the manufacture of evolocumab drug substance are acceptable from a CGMP perspective.*

—Satisfactory—

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

3.2.S.2.2.1 Batch Scale and Definition

(b) (4)

3.2.A. Appendices

3.2.A.1. Facility and Equipment

Evolocumab drug substance is manufactured a [REDACTED] (b) (4)
[REDACTED] The flow of product, raw material, and personnel are provided and were assessed during the PLI from a cross contamination control perspective.

Review comments: Facility and equipment information was assessed during the pre-license inspection [REDACTED] (b) (4)

—Satisfactory—

3.2.A.2. Adventitious Agents Safety Evaluation

Review comments: This section will be reviewed by OBP.

3.2.R. Regional Information

Review comments: Regional information was adequately provided and additional assessment is deferred to OBP for review.

Environmental Assessment:

As per a statement in module 1.12.14 of original BLA, Evolocumab is subject to a categorical exclusion under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31 (c), based on consideration of its effects when exposed to the environment. Evolocumab is considered to be a nonhazardous, biodegradable product. Patients injected with Evolocumab are expected to fully catabolize it with negligible excretion of intact, biologically-active protein from the body. Any breakdown products are not expected to remain in the environment for any significant period as a biologically active protein because of their susceptibility to biodegradation by a wide range of environmental microflora. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment.

—Satisfactory—

Conclusion:

- I. Sections 3.2.S of the BLA pertaining to microbial control of the drug substance were reviewed. The BLA, as amended, is recommended for approval from a microbiology product quality.
- II. Product specific CMC information and data should be reviewed by OBP.
- III. There are no inspection follow up issues.

CC: OPQ/OPF/DIA/Shanks
OPQ/OPF/DMA/Hughes

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

BLA/NDA Number: 125522 **Applicant:** Amgen Inc.

Stamp Date: 8/27/2014

Established/Proper Name: **BLA/NDA Type:** Standard
Evolocumab / N/A

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

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed <input type="checkbox"/> including list of all establishment sites and their registration numbers	Y N	Defer to BMAB: Registration (FEI) number for [REDACTED] ^{(b) (4)} facility is not provided.
Comprehensive Table of Contents	N	High level content of the BLA is clear based on eCTD format.
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: <input type="checkbox"/> PI –non-annotated <input type="checkbox"/> PI –annotated <input type="checkbox"/> PI (electronic) <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Insert <input type="checkbox"/> package and container <input type="checkbox"/> diluent <input type="checkbox"/> other components <input type="checkbox"/> established name (e.g. USAN) <input type="checkbox"/> proprietary name (for review)	Y Y Y N Y Y N Y Y Y	Deferred to clinical reviewer: The need of M/G will be decided during the course of the review. Not applicable

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	
<input type="checkbox"/> all electronic submission components		

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

Examples of Filing Issues	Yes?	If not, justification, action & status
usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	N	Not applicable

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	eCTD formatting is clearly defined.
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]		
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	
<input type="checkbox"/> Novel Excipients	Y	
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	eCTD formatting is clearly defined.
Drug Substance [3.2.S]		
<input type="checkbox"/> general info		
<input type="radio"/> nomenclature	Y	
<input type="radio"/> structure (e.g. sequence, glycosylation sites)	Y	
<input type="radio"/> properties	Y	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control		
<input type="radio"/> batch numbering and pooling scheme	Y	
<input type="radio"/> cell culture and harvest	Y	
<input type="radio"/> purification	Y	
<input type="radio"/> filling, storage and shipping	Y	
<input type="checkbox"/> control of materials		
<input type="radio"/> raw materials and reagents	Y	
<input type="radio"/> biological source and starting materials	Y	
<input type="radio"/> cell substrate: source, history, and generation	Y	
<input type="radio"/> cell banking system,	Y	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<p>including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</p> <ul style="list-style-type: none"> <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation <input type="checkbox"/> Validation of aseptic processing (media simulations) <input type="checkbox"/> Environmental Monitoring Program <input type="checkbox"/> Lyophilizer sterilization validation <input type="checkbox"/> Other needed validation data (hold times) <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) <input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results 		
<p>Other components to be marketed (full description and supporting data, as listed above):</p> <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part 	<p>Y</p> <p>N</p>	<p>Not applicable</p>

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

Examples of Filing Issues	Yes?	If not, justification, action & status
in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y Y Y	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

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

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

No issues sent this time.

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

sangbong.lee@fda.hhs.gov Digitally signed by sangbong.lee@fda.hhs.gov
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Date: 2014.10.14 13:58:35 -04'00' Sang Bong Lee

Product Quality Reviewer Date

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=Peop, e=0.9.2342.19200300.100.1.1=0012957817,
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Date: 2014.10.14 13:17:01 -04'00' Bazarragchaa Damdinsuren

Product Quality Reviewer Date

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o=9.2342.19200300.100.1.1=200601863,
Date: 2014.10.14 23:10:31 -04'00' Chana Fuchs

Team Leader Date

Sarah B. Kennett -S Digitally signed by Sarah B. Kennett 5
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Date: 2014.10.22 11:32:08 -04'00' Sarah Kennett

Review Chief Date

Kathleen A. Clouse Strebel -S Digitally signed by Kathleen A. Clouse Strebel -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
o=9.2342.19200300.100.1.1=1300054511,
cn=Kathleen A. Clouse Strebel -S
Date: 2014.10.22 13:42:56 -04'00' Kathleen A. Clouse

Division Director Date