

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125277

MICROBIOLOGY REVIEW(S)



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

Date: 16 October 2009
To: Administrative File, STN 125277
From: Anastasia G. Lolas, Microbiology Reviewer, OC/DMPQ/MAPCB/BMT AL 10/16/09
Through: Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/MAPCB/BMT PHH 10/20/09
Subject: New Biologics License Application
Applicant: Dyax Corporation (Cambridge, MA)
License: #1789
Facility: Drug Substance – Avecia Biologics, Billingham, UK (FEI: 3007182567)
Drug Product – Hollister-Stier Laboratories, LLC, Spokane, WA (CFN: 3010477)
Product: Kalbitor™ (ecallantide)
Dosage: Sterile liquid in a single-dose 2 mL glass vial (1 mL fill), 10 mg/mL for subcutaneous injection
Indication: Treatment of hereditary angioedema
Due date: 01 December 2009

Recommendation for Approvability: BLA 125277 is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. The status of all manufacturing and testing facilities is acceptable.

Review Summary

Dyax, Inc. submitted BLA STN 125277 to license Kalbitor™ (ecallantide) Injection and the associated drug substance and drug product manufacturing processes. This is a resubmission (seq 0035, dated 31-May-2009) of the original application to respond to deficiencies listed in the 25-Mar-2009 complete response letter. STN 125277 has an orphan drug status and is a priority review with a user fee date of 01-Dec-2009. Primary reviews are due on 23-Oct-2009 while secondary reviews are due on 30-Oct-2009.

STN 125277 is an electronic submission in CTD format. It includes responses to the 4 microbiology deficiencies included in the complete response letter. A Type A meeting was held with Dyax on 14-May-2009 to provide clarification on the questions listed in the complete response letter. This review assesses Dyax's responses to the 4 microbiology items. See

Microbiology Review dated 03-Mar-2009 for an assessment of the CMC-Microbiology sections of the original submission.

The following submissions related to CMC and product quality microbiology were reviewed: 31-May-2009 (seq 0035), 10-Jun-2009 (seq 0036), 29-Jun-2009 (seq 0037), 21-Jul-2009 (seq 0038), and 12-Aug-2009 (seq 0039).

The compliance status of all manufacturing and testing facilities is acceptable.

Review Narrative

1. COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3

S DRUG SUBSTANCE

The drug substance is ecallantide, a recombinant protein expressed in a yeast production system (*Pichia pastoris*). It has 60 amino acid residues with 3 intramolecular disulfide bonds for a total molecular weight of 7054 Daltons. Ecallantide drug substance is not sterile but has a (b) (4) specification. It is stored at -20±5°C in sterile USP Class VI (b) (4)

The proposed pH is (b) (4) with a shelf-life of 36 months.

The manufacturing process for ecallantide consists of (b) steps: (b) (4)

The bioburden level for ecallantide is (b) (4) as tested per Ph. Eur. 2.6.12. The bacterial endotoxins specification is (b) (4) as tested per USP <85> and Ph. Eur. 2.6.14.

P DRUG PRODUCT

DX-88 or Kalbitor™ is a sterile, preservative-free, isotonic solution provided in a single-dose 2 mL Type I (b) (4) glass vial (b) (4) with 1 mL fill. The vial is sealed with a (b) (4) stopper (b) (4)) and a (b) aluminum seal with a flip-off cap. Secondary packaging consists of a cardboard box coated with an aqueous UV gloss to protect the product from light. The product strength is 10 mg/mL and is intended for subcutaneous administration. Table 1 presents the composition of Kalbitor™. No excipients are added

TABLE 2. Drug substance and drug product manufacturing and testing sites

Establishment	Reg. Number	Responsibilities
Avecia Biologics P.O. Box 2, Belasis Avenue Billingham, Cleveland TS23 1YN United Kingdom	3007182567	Drug substance manufacture, in-process, release & stability testing, cell bank manufacture & storage, drug product stability testing (except sterility & particulates)
Hollister-Stier Laboratories, LLC 3525 North Regal Street Spokane, WA 99207	3010477	Drug product manufacture, in-process and release testing (pH, osmolality, sterility & particulates), labeling & packaging
Dyax Corp. 300 Technology Square Cambridge, MA 02139	3007220955	Application holder, batch disposition

(b) (4)

Complete Response Letter – Microbiology Questions

1. *Sufficient information regarding depyrogenation of 2 mL glass vials has not been provided.*
 - a. *Describe the load configuration that includes the 2 mL glass vial. The January 16, 2009 amendment does not identify this load.*
 - b. *Provide the minimum lethality values for the loads validated and for the load that includes the 2 mL glass vial.*

c. Describe the minimum load configurations and rationale.

(b) (4)

SATISFACTORY

Reviewer's Comments: The additional information regarding depyrogenation of 2 mL vials demonstrates that the depyrogenation process in the batch oven is effective at achieving a 3-log reduction in endotoxin. Results are consistent. The 2 mL vial load is bracketed by the matrix approach based on mass.

2. Validation studies for stopper sterilization were performed using biological indicator spore strips and ampoules. It is recommended that studies be performed using a biological indicator spore suspension directly inoculated onto the stoppers due to the variation in D-values that may result from using indicator spore strips and ampoules. Alternatively, you may provide data to demonstrate that the bioburden of incoming stoppers has resistance that does not exceed that of the biological indicator used in the validation studies.

Dyax provides data for stopper loads used in the ecallantide manufacturing process. It is stated that the validation approach using spore strips has been implemented for (b) stopper

sterilization cycles for the last () years. (b) (4)

(b) (4) This corresponds to a theoretical kill time of (b) (4) (b) (4) load configurations have been qualified for the (b) (4) ready-to-sterilize stoppers using sub-process parameters of (b) (4).

The submission provides the minimum lethality values achieved and the BI calculated kill time for qualified ecallantide stopper loads. The same data are presented as in the original submission. Lethality values were (b) (4) for sub-process cycles including PQ Study 06-786-A-1 "Equivalency Evaluation of Dyax Components – Stopper Sterilization Confirmation Study" with a calculated kill time of (b) (4).

See also microbiology review dated 03-Mar-2009.

In addition, bioburden data for incoming stoppers are presented for the period Jan 2008-Apr 2009 for (b) (4) different lots. (b) (4) different lots of (b) (4) ready-to-sterilize stoppers including 1 lot used for ecallantide manufacture were tested. All lots resulted in 0 CFU/stopper).

SATISFACTORY

Reviewer's Comments: Validation and requalification runs demonstrate that the sterilization process is effective and reproducible for all load configurations. Incoming stoppers do not present bioburden and as a result, there is low risk for the presence of microorganisms more resistant than the BI.

3. *With regard to assay sensitivity, the sensitivity of the dye ingress container-closure integrity test has not been provided. Provide the smallest volume of dye that can be detected under the provided test conditions.*

The submission includes the validation report AVR0198 for the dye ingress container-closure integrity test performed by Avecia in accordance with USP <1225>. The method is based on USP <381> and Annex C of ISO 8362-2:2008. The sensitivity of the assay is (b) (4) of dye as detected by visual observation. This volume corresponds to (b) (4) and (b) (4).

Method AM880 was evaluated for precision, robustness, sensitivity and system suitability as per Validation Protocol QAAVP0198. Precision was evaluated (b) (4) times using (b) (4) sets of (b) (4) vials. One set of vials had been compromised with a 30G needle that had been left in the septum. Robustness was assessed (b) (4) times using (b) (4) sets of vials for each of () runs. One set of vials was compromised as described above. One run was performed with reduced pressure to (b) (4) bar, 1 run was performed with reduced time under pressure (b) (4) and 1 run was performed with reduced time for restoring atmospheric pressure (b) (4). The acceptance criteria were no detection of blue dye ingress in the sealed vials and dye ingress in the compromised vials as determined by visual inspection. All the criteria were met. The sensitivity of the method was evaluated by preparing 10 vials with different concentration of methylene blue dye. The vials contained 1.15 mL water to which 1-10 µL of 0.01% w/v dye was added to result in concentrations of 1.0-10.0 µL. Each vial was examined by 3 different analysts against a placebo (water only) vial for dye ingress. All 3 analysts

detected the dye at (b) (4). The acceptance criterion was for all analysts to detect dye ingress for the (b) (4) vial and this was achieved.

SATISFACTORY

4. *As provided for by 21 CFR 610.9, submit a formal request to waive the requirement for a*
(b) (4)



SATISFACTORY

**2. COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1**

PACKAGE INSERT

The words (b) (4) have been added to the side panel of the vial carton box. It is also stated that the product is single-use. The package insert has all the necessary information regarding (b) (4). The vial label does not state (b) (4). However, there is not much space for this to be added.

Environmental Assessment

See the microbiology review of the original submission.

cGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the submitted sites. There are no pending or ongoing compliance actions to prevent approval of STN 125277/0 at this time. The status for the sites is the following:

Establishment	FEI	Inspection Date	Classification	Profile
Avecia Biologics P.O. Box 2, Belasis Avenue Billingham, Cleveland TS23 1YN United Kingdom	3007182567	Jan 5-9, 2009	VAI	(b) (4) Acceptable
Hollister-Stier Laboratories, LLC 3525 North Regal Street Spokane, WA 99207	3010477	Mar 16-26, 2009	VAI	(b) (4): Acceptable

Dyax Corp.
300 Technology Square
Cambridge, MA 02139

3007220955 No GMP inspectional history; Compliance evaluation
not necessary

(b) (4)

Conclusion

- I. The STN 125277/0 resubmission was reviewed from a microbial control, sterility assurance and microbiology product quality perspective and is recommended for approval.
- II. With the exception of the microbiological aspect, the resubmission should be reviewed by OBP/DTP.
- III. There are no follow-up inspection items.

Cc: OC/DMPQ/WO Bldg 51, Lolas
OC/DMPQ/WO Bldg 51, Hughes
OC/DMPQ/WO Bldg 51, Blue Files (STN 125277)
OPS/OBP/NIH Bldg N29A, Lee
OND/ODEII/DPAP/WO Bldg 22, Jackson

Archived File: S:\archive\BLAs\125277\125277.0.rev.mem.BLA.10-16-09.doc

STN 125277, Dyax Corporation, Kalbitor™ (ecallantide) Injection

From: Stock, Marisa
Sent: Friday, October 16, 2009 8:47 AM
To: Lolos, Anastasia
Cc: CDER-TB-EER
Subject: RE: BLA 125277 resubmission

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation for the TB-EER below. Please see the original message below to find the updated compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of BLA 125277 at this time.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Lolos, Anastasia
Sent: Thursday, July 16, 2009 4:54 PM
To: CDER-TB-EER
Subject: BLA 125277 resubmission

BLA 125277 has been resubmitted by Dyax Corporation following a complete response letter. The date of submission is 31-May-2009 and the user fee date is 01-Dec-2009. This is a priority review for Kalbitor (ecallantide), an orphan drug product. Please conduct an establishment evaluation of the following sites:

Avecia Biologics (Testing and storage of raw materials and components, manufacture of drug substance, in-process, release, and stability testing, storage of stability samples, manufacturer and storage of cell banks)

Advanced Biologics Centre 5000 L Facility
PO Box 2, Belasis Avenue
Billingham, Cleveland TS23 1YN UK
FEI: 3007182569

A pre-license inspection for ecallantide was conducted January 5-9, 2009 and classified VAI. The (b) (4) profile was covered and is acceptable.

Hollister-Stier Laboratories, LLC (Manufacture of drug product, in-process and release testing, labeling and packaging)

3525 North Regal Street
Spokane, WA 99207
FEI: 3010477

Inspected March 16-26, 2009 and classified VAI. The SVS profile was covered and is acceptable.

(b) (4)

(b) (4)

(b) (4)

Dyax Corporation (Batch disposition)

300 Technology Square

Cambridge, MA

FEI: 3007220955

No GMP inspectional history. Compliance evaluation not necessary.

(b) (4)

of the CDER.

Thank you,

Anastasia G. Lolas, M.S.

Microbiologist

Biotech Manufacturing Team/MAPCB/DMPQ

Office of Compliance, CDER

White Oak Bldg 51, Room 4216

301-796-1566

51 pp withheld immediately following this page as (b)(4) CCI/TS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

Date: 03 March 2009
To: Administrative File, STN 125277
From: Anastasia G. Lolas, Microbiology Reviewer, OC/DMPQ/MAPCB/BMT AL 3/3/09
Through: Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/MAPCB/BMT PH 3/3/09
Coki Cruz, Acting Branch Chief, OC/DMPQ/MAPCB C. Cruz for C. Cruz 2/23/09
Subject: New Biologics License Application
Applicant: Dyax Corporation (Cambridge, MA)
Facility: Drug Substance – Avecia Biologics, Billingham, Cleveland TS23 1YN, UK (FEI: 3007182567)
Drug Product – Hollister-Stier Laboratories, LLC, Spokane, WA (CFN: 3010477)
Product: Kalbitor™ (ecallantide)
Dosage: Sterile liquid in a single-dose 2 mL glass vial (1 mL fill), 10 mg/mL for subcutaneous injection
Indication: Treatment of hereditary angioedema
Due date: 23 March 2009

Recommendation for Approvability: BLA 125277 is not recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. There are 4 deficiencies and 1 comment. The Avecia drug substance manufacturing site was inspected on 1/5-1/9/2009 and found acceptable, VAI with one FDA 483 observation. Avecia's 20-JAN-2009 response has been reviewed and found acceptable. An inspection waiver memo is attached to the review for the drug product site, Hollister-Stier Laboratories, LLC.

Review Summary

Dyax, Inc. submitted BLA 125277 to license Kalbitor™ (ecallantide) Injection and the associated drug substance and drug product manufacturing processes. The application has an orphan drug status and is a priority review with a PDUFA user fee date of 23-MAR-2008.

BLA 125277 is an electronic submission in CTD format submitted in 3 parts as agreed to with the Division of Pulmonary and Allergy Products in the pre-BLA meeting of 30-OCT-2007. BMT did not participate in the pre-BLA meeting. Module 3 was first submitted on 31-DEC-2007. The

other modules followed on 27-MAR-2008 and 23-SEP-2008. Additional quality information was submitted in the third and last part of the submission.

Dyax Corp. initially submitted a production schedule for February 23 to April 3, 2009 which would not help meet the GRMP deadlines for this priority BLA with a user fee date of March 23, 2009. The application was recommended for refuse-to-file by OBP. After several teleconferences with the applicant, including internal communication with OND, OBP and DMPQ, a revised production schedule was submitted to the BLA on 18-NOV-2008 for early January.

Any CMC CTD sections that are not listed in this review are deferred to the OBP reviewers.

The following amendments related to CMC and product quality microbiology were reviewed: 23-SEP-2008 (sequence 0002), 10-OCT-2008 (sequence 0003), 18-NOV-2008 (sequence 0006), 09-DEC-2008 (sequence 0008), 23-DEC-2008 (sequence 0013) and 16-JAN-2009 (sequence 0019).

A pre-license inspection of the drug substance manufacturing site, Avecia Biologics (Billingham, UK) was conducted between 05-JAN and 09-JAN-2009 and was classified as VAI. One FDA 483 item was noted regarding the sampling of water and environmental monitoring samples. Avecia's 20-JAN-2009 response has been reviewed and found acceptable.

Review Narrative

1. COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3

S DRUG SUBSTANCE

S.1 General Information

The drug substance is ecallantide, a recombinant protein expressed in a yeast production system (*Pichia pastoris*). It has 60 amino acid residues with 3 intramolecular disulfide bonds for a total molecular weight of 7054 Daltons. Ecallantide drug substance is not sterile but has (b) (4) specification. It is stored at $-20\pm 5^{\circ}\text{C}$ in sterile USP Class VI (b) (4).

(b) (4) The proposed pH is (b) (4) The proposed shelf-life is 36 months.

S.2 Manufacture

S.2.1 Manufacturers

Avecia Biologics (Avecia), Advanced Biologics Centre 5000 L Facility (ABC5000), P.O. Box 2, Belasis Avenue, Billingham, Cleveland TS23 1YN, United Kingdom is the contract manufacturer for ecallantide. Avecia (FEI: 3007182567) is also responsible for testing and storage of raw materials and components, in-process, release and stability testing, storage of stability samples and manufacture and storage of cell banks. (b) (4) is responsible for secondary storage of cell banks and storage of the drug substance

prior to drug product manufacture. In addition, (b) (4) is used for storage of drug substance prior to drug product manufacture (b) (4) (b) (4) performs the (b) (4) analysis for release testing.

S.2.2 Description of the Manufacturing Process and Process Controls

(b) (4)



Microbial controls were assessed during the inspection (see EIR).

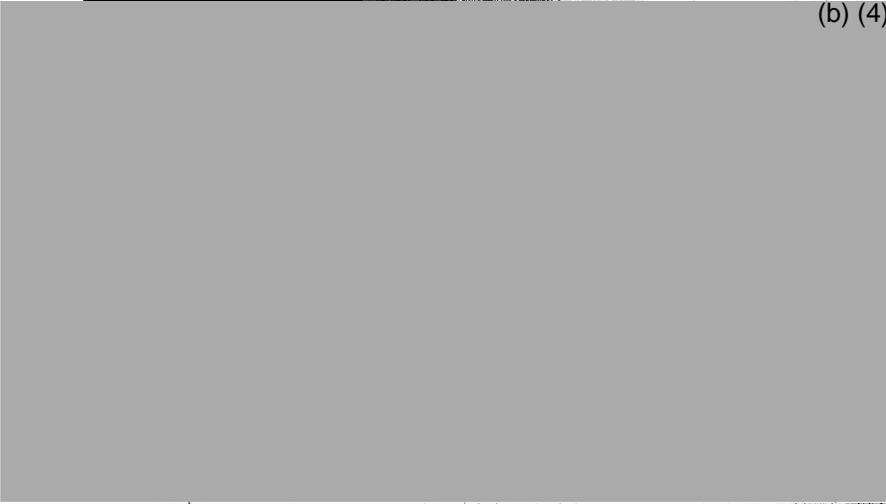
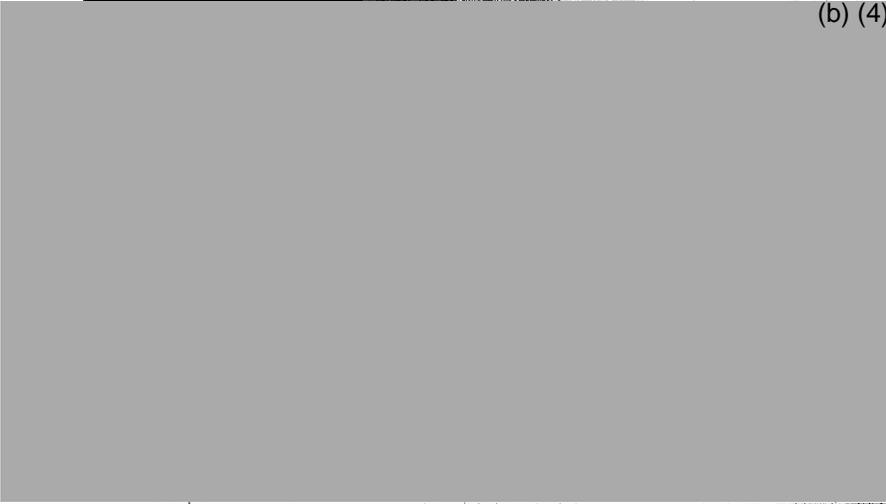
SATISFACTORY

21 PP WITHHELD IMMEDIATELY AFTER THIS PAGE AS (B)
(4) CCI/TS

Review Comment: The applicant's claim is satisfactory as ecallantide is a protein found in natural systems.

eGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the submitted sites. There are no pending or ongoing compliance actions to prevent approval of BLA 125277 at this time. The status for the sites is the following:

Establishment	FEI	Inspection Date	Classification	Profile
Avecia Biologics P.O. Box 2, Belasis Avenue Billingham, Cleveland TS23 1YN United Kingdom	3007182567	1/5~9/2009	VAI	(b) (4)
			(b) (4)	NAI
				NAI
				NAI
Hollister-Stier Laboratories, LLC 3525 North Regal Street Spokane, WA 99207	3010477	1/6~13/2009	VAI	
	6/19~7/2/2008	NAI/VAI		
	(b) (4)	3006651658	1/18~21/2008	VAI
		2529019	11/2~3/2004	NAI

STN 125277, Dyax Corporation

Conclusion

- I. STN 125277/0 with amendments was reviewed from a microbial control, sterility assurance perspective and microbiology product quality perspective and is not recommended for approval. There are 4 deficiencies and 1 comment to be sent to the applicant.
- II. With the exception of the microbiological aspect, the application should be reviewed by an OBP/DTP reviewer.
- III. The next inspection of the Hollister-Stier facility should verify the filtration conditions and holding times approved in this BLA and that bioburden meets the acceptance criteria described in the BLA.

Cc: OC/DMPQ/WO Bldg 51, Lolas
OC/DMPQ/WO Bldg 51, Hughes
OC/DMPQ/WO Bldg 51, Cruz
OC/DMPQ/WO Bldg 51, Blue Files (STN 125277)
OPS/OBP/NIH Bldg N29A, Lee
OND/ODEII/DPAP/WO Bldg 22, Jackson

Archived File: S:\archive\BLAs\125277\STN125277.0.rev.mem.BLA.03-03-09.doc

Part B – Product/CMC/Facility 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	
Quality overall summary [2.3]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Drug Substance	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Drug Product	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Facilities and Equipment	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	<input type="radio"/> Y <input type="radio"/> N	Defer to OBP
<input type="checkbox"/> Novel Excipients	<input type="radio"/> Y <input type="radio"/> N	Defer to OBP
<input type="checkbox"/> Executed Batch Records	<input type="radio"/> Y <input checked="" type="radio"/> N	Some batch records are provided in Mod 3
<input type="checkbox"/> Method Validation Package	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Comparability Protocols	<input type="radio"/> Y <input checked="" type="radio"/> N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="radio"/> nomenclature		
<input type="radio"/> structure (e.g. sequence, glycosylation sites)		
<input type="radio"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> description of manufacturing process	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="radio"/> batch numbering and pooling scheme		
<input type="radio"/> cell culture and harvest		
<input type="radio"/> purification		
<input type="radio"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="radio"/> raw materials and reagents		
<input type="radio"/> biological source and starting materials		
<input type="radio"/> cell substrate: source, history, and generation		
<input type="radio"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="radio"/> justification of specifications		
<input type="radio"/> analytical method validation		
<input type="radio"/> reference standards		
<input type="radio"/> stability		
<input type="checkbox"/> process validation (prospective plan, results, analysis, and	<input checked="" type="radio"/> Y <input type="radio"/> N	

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin) <input type="checkbox"/> control of drug product (justification of specifications; analytical method validation) <input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity ○ administration device(s) <input type="checkbox"/> stability <ul style="list-style-type: none"> □ summary □ post-approval protocol and commitment □ pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	(Y) N (Y) N (Y) N	Additional detail may be needed on description of microbiological methods Defer to OBP, references to DMFs provided Microbiology only. Post-approval protocol does not include cont-clos integrity test at 24 months even though it is performed at 12 and 36 months
Diluent (vials or filled syringes) [3.2P'] <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <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"> ○ 3 consecutive lots ○ other needed validation data <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	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	N/A

CTD Module 3 Contents	Present?	If not, justification, action & status
<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 <input type="checkbox"/> closure integrity <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 	Y N Y N	
Other components to be marketed (full description and supporting data, as listed above): <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit) 	Y N Y N	N/A
Appendices for Biotech Products [3.2.A] <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation and storage <input type="checkbox"/> sterilization of equipment and materials <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	Y N Y N Y N	Defer to OBP Defer to OBP
USA Regional Information [3.2.R] <input type="checkbox"/> executed batch records <ul style="list-style-type: none"> <input type="checkbox"/> method validation package <input type="checkbox"/> comparability protocols 	Y N Y N Y N	Defer to OBP

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	<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"/> all electronic submission components usable	<input checked="" type="radio"/> Y <input type="radio"/> N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	<input checked="" type="radio"/> Y <input type="radio"/> N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	<input checked="" type="radio"/> Y <input type="radio"/> N	
includes data demonstrating consistency of manufacture	<input checked="" type="radio"/> Y <input type="radio"/> N	
includes complete description of product lots and manufacturing process utilized for clinical studies	<input checked="" type="radio"/> Y <input type="radio"/> N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	<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	
certification that all facilities are ready for inspection	<input checked="" type="radio"/> Y <input type="radio"/> N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	<input checked="" type="radio"/> Y <input type="radio"/> N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of Filing Issues	Yes?	If not, justification, action & status
that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility <input type="checkbox"/> <input type="checkbox"/>	<input checked="" type="radio"/> Y <input type="radio"/> N <input type="radio"/> Y <input checked="" type="radio"/> N <input checked="" type="radio"/> Y <input type="radio"/> N	N/A
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	<input checked="" type="radio"/> Y <input type="radio"/> N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	<input checked="" type="radio"/> Y <input type="radio"/> N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	<input checked="" type="radio"/> Y <input type="radio"/> N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	<input checked="" type="radio"/> Y <input type="radio"/> N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	N/A

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).

The recommendation is to file BLA 125277. However, additional detail may be requested during the review cycle on sterilization validation studies and container-closure integrity studies.

Recommendation (circle one): File RTF

For Applications: Were any potential review issues identified for the day 74 letter? Yes No

Reviewer: [Signature] 10/28/08
 (signature/ date) Type (circle one): Product (Chair) Facility (DMPQ)

Concurrence:
 Branch/Lab Chief: [Signature] 10/29 Division Director: [Signature] 10/29/2008
 (signature/ date) (signature/ date)