

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125469Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA: 125469/0
Applicant: Eli Lilly and Company
US License Number: 1891
Submission Reviewed: Original BLA
Product: Dulaglutide (Trulicity)
Indication: Improved glycemic control of type 2 diabetes mellitus
Dosage Form: The drug product is a clear, colorless, sterile solution for subcutaneous injection supplied in 0.75 mg/0.5 ml and 1.5 mg/0.5 ml dosage strengths. The drug product is supplied in a single-use prefilled syringe or in a single-use pen injector.
Manufacturing Sites: Eli Lilly, Indianapolis, IN (FEI: 1819470)

(b) (4)

FDA Receipt Date: 18 September 2013
Action Date: 18 September 2014

Conclusion and Approvability Recommendation

The drug product portion of the BLA was reviewed from a product quality microbiology perspective and is recommended for approval. The sponsor has agreed to fulfill the following PMC:

- Explore alternative test methods and to develop a more suitable endotoxin release test for dulaglutide drug substance and drug product.

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(b) (4)

POST-MARKETING COMMITMENT

Drug Product Quality Microbiology PMCs for BLA 125469

The sponsor has agreed to the following PMCs:

1. Provide data from one additional (b) (4) batch to support the (b) (4) hour hold time limit (b) (4). The data will be provided in the first annual report.
2. Provide summary data from performance qualification shipping studies for shipment of the SFS and PFS from (b) (4) to Eli Lilly in the summer and winter. The data will be provided in the first annual report.
3. Explore alternative test methods and to develop a more suitable endotoxin release test for dulaglutide drug substance and drug product. The PMC study protocol will be provided by March 2015. The PMC final study report will be submitted by December 2016.

Additional Information

Environmental Assessment

The sponsor claims a categorical exclusion for this application pursuant to 21 CFR 25.25 (d) based on the exclusion allowed by 21 CFR 25.31 (c). The sponsor indicates that the actions associated with this submission do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

CGMP Status

Please refer to the TB-EER response in DARRTS.

Conclusion

- I. The drug product portion of the BLA was reviewed from a product quality microbiology perspective and is recommended for approval. There are three PMCs.
- II. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.
- III. A pre-license inspection of the Eli Lilly site was conducted from 21-25 July 2014.

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/s/

COLLEEN THOMAS
09/10/2014

PATRICIA F HUGHES TROOST
09/10/2014



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

Date: 9/5/2014
To: Administrative File, **STN 125469/0**
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Addendum to review memo for New Biologic License Applications (BLA) STN125469/0 dated 5/12/2014
Applicant: Eli Lilly and Company
US License: 1891
Facility: Eli Lilly S.A. – Irish Branch
Kinsale, County Cork, Ireland
FEI: 3002806888
Product: dulaglutide (Trulicity)
Dosage: 0.75 mg/0.5 mg and 1.5 mg/0.5 mL, solution for subcutaneous injection in a prefilled syringe or an auto-injector
Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
PDUFA date: September 18, 2014

Recommendation: The drug substance section of this BLA, as amended, is recommended for approval from product quality microbiology perspective with the following post-market commitment:

Explore alternative test methods and develop a more suitable endotoxin release test for dulaglutide drug substance and drug product.

Review Summary

This review amends the drug substance microbiology product quality review memo for Eli Lilly's BLA STN125469/0 dated 5/12/2014 with new information and data submitted by the applicant [amendments dated 5/30/2014 (sequence 25), 6/18/2014 (Sequence 30), 6/27/2014 (Sequence 32), 8/5/2014 (Sequence 34), and 8/25/2014 (Sequence 35)] pertaining to:

- Endotoxin hold-time study data for the (b) (4) drug substance
- Additional bioburden and endotoxin qualification data for the (b) (4) intermediate samples
- Change management protocol (provided in 3.2.R)

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PMC:

Explore alternative test methods and develop a more suitable endotoxin release test for dulaglutide drug substance and drug product.

Conclusion

The drug substance section of this BLA, as amended, is recommended for approval from product quality microbiology perspective with the following post-market commitment:

Explore alternative test methods and develop a more suitable endotoxin release test for dulaglutide drug substance and drug product.

Cc: Chi
Hughes
Abolade

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/s/

BO CHI
09/05/2014

PATRICIA F HUGHES TROOST
09/05/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA: 125469/0
Applicant: Eli Lilly and Company
US License Number: 1891
Submission Reviewed: Original BLA
Product: Dulaglutide (Trulicity)
Indication: Improved glycemic control of type 2 diabetes mellitus
Dosage Form: The drug product is a clear, colorless, sterile solution for subcutaneous injection supplied in 0.75 mg/0.5 ml and 1.5 mg/0.5 ml dosage strengths. The drug product is supplied in a single-use prefilled syringe or in a single-use pen injector.
Manufacturing Sites: Eli Lilly, Indianapolis, IN (FEI: 1819470)
[REDACTED] (b) (4)
FDA Receipt Date: 18 September 2013
Action Date: 18 September 2014

Conclusion and Approvability Recommendation

The product quality microbiology review of this BLA is not yet complete because data from the [REDACTED] (b) (4) comparison study has not yet been submitted. The data will be submitted by 29 August 2014. If the [REDACTED] (b) (4) is able to detect endotoxin in the drug product, then the [REDACTED] (b) (4) will be required for drug product release testing until an

alternative method is developed. In addition, there will be a PMC for endotoxin testing of the drug product.

If the sponsor agrees to the endotoxin release test strategy proposed by the Agency and agrees to fulfill the endotoxin testing PMC, the drug product portion of the BLA will be recommended for approval from a microbial control perspective. This information will be reviewed in an addendum to the review memo.

(b) (4)



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Drug Product Quality Microbiology PMCs

Reviewer's comment: The sponsor has already agreed to perform the first two PMC studies. Notification of the third PMC study was sent to the sponsor in an information request.

1. Provide data from one additional (b) (4) batch to support the (b) (4) hour hold time limit (b) (4) Provide this data in the first annual report.
2. Provide summary data from performance qualification shipping studies for shipment of the SFS and PFS from (b) (4) to Eli Lilly in the summer and winter. Provide this data in the first annual report.
3. Conduct post-marketing studies to understand the mechanism of low endotoxin recovery in the formulated (b) (4) drug substance and drug product. Based on the results of these studies, modify the endotoxin release test and/or determine the suitability of alternative endotoxin test methods.

Additional Information

Environmental Assessment

The sponsor claims a categorical exclusion for this application pursuant to 21 CFR 25.25 (d) based on the exclusion allowed by 21 CFR 25.31 (c). The sponsor indicates that the actions associated with this submission do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

CGMP Status

Please refer to the TB-EER response in DARRTS.

Conclusion

- II. The product quality microbiology review of this BLA is not yet complete because data from the (b) (4) comparison study has not yet been submitted. The data will be submitted by 29 August 2014. If the (b) (4) is able to detect endotoxin in the drug product, then the (b) (4) will be required for drug product release testing until an alternative method is developed. In addition to the PMCs the sponsor has already agreed to fulfill, there is a PMC for endotoxin testing of the drug product. If the sponsor agrees to the endotoxin release test strategy proposed by the Agency and agrees to fulfill the endotoxin testing PMC, the drug product portion of the BLA will be recommended for approval from a microbial control perspective. This information will be reviewed in an addendum to the review memo.
- III. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.
- IV. A pre-license inspection of the Eli Lilly site was conducted from 21-25 July 2014.

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/s/

COLLEEN THOMAS
08/14/2014

PATRICIA F HUGHES TROOST
08/14/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
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BLA: 125469/0
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Manufacturing Sites: Eli Lilly, Indianapolis, IN (FEI: 1819470)

(b) (4)

FDA Receipt Date: 18 September 2013
Action Date: 18 September 2014

Conclusion and Approvability Recommendation

The BLA was reviewed from a product quality microbiology perspective, but the review is not yet complete because discussions with the sponsor regarding the endotoxin control strategy for the drug product are still ongoing. The endotoxin control strategy will be reviewed in an addendum to this memo.

In addition, the sponsor has agreed to perform the following studies. The PMC status

1. Provide data from one additional (b) (4) batch to support the (b) (4) hour hold time limit (b) (4).
The sponsor has agreed to provide this data in the first annual report.
2. Provide summary data from performance qualification shipping studies for shipment of the SFS and PFS from (b) (4) to Eli Lilly in the summer and winter. The sponsor has provided study protocols and completion dates. The protocols have been reviewed. The sponsor will be asked to submit the data in the first annual report.

3.

(b) (4)

(b) (4)

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/s/

COLLEEN THOMAS
06/20/2014

PATRICIA F HUGHES TROOST
06/20/2014



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

Date: 5/12/2014
To: Administrative File, STN 125469/0
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Applications (BLA)
Applicant: Eli Lilly and Company
US License: 1891
Facility: Eli Lilly S.A. – Irish Branch
Kinsale, County Cork, Ireland
FEI: 3002806888
Product: dulaglutide
Dosage: 0.75 mg/0.5 mg and 1.5 mg/0.5 mL, solution for subcutaneous injection in a prefilled syringe or an auto-injector
Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
PDUFA date: September 18, 2014

Recommendation: The approval of the drug substance part of this BLA is pending until the following information and data have been submitted and reviewed:

- Endotoxin hold-time study data for the (b) (4) drug substance
- Additional bioburden and endotoxin qualification data for (b) (4) intermediate samples

Review Summary

Eli Lilly has submitted this Biologics License Application (BLA) for dulaglutide to improve glycemic control in adults with type 2 diabetes mellitus. The drug substance (DS) is manufactured at the Eli Lilly S.A. facility at Kinsale, Ireland. The drug product (DP) is manufactured at Eli Lilly and Company in Indianapolis, IN and (b) (4). The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of dulaglutide drug substance from microbiology perspective.

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/s/

BO CHI
05/22/2014

PATRICIA F HUGHES TROOST
05/22/2014

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

BLA/NDA Number:
STN125469/0

Applicant: Eli Lilly and
Company

Stamp Date:

Established/Proper Name:
dulaglutide

BLA/NDA Type: BLA standard

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 Y	
Comprehensive Table of Contents	Y	
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 N Y N Y N Y N Y N Y N Y N Y N Y N Y N	Defer to OND.

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

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

Examples of Filing Issues	Yes?	If not, justification, action & status
shared or divided manufacturing arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<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]	Y	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	
<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)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y	
<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	Y	Defer to OBP.
<input type="radio"/> raw materials and reagents	N	
<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		

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> control of critical steps and intermediates <ul style="list-style-type: none"> ○ justification of specifications ○ stability 	Y	
<input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions)	Y	
<input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	Defer to OBP.
<input type="checkbox"/> characterization of drug substance	Y N	Defer to OBP.
<input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ specifications <ul style="list-style-type: none"> ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses 	Y	
<input type="checkbox"/> reference standards	Y N	Defer to OBP.
<input type="checkbox"/> container closure system	Y	
<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"> ○ protocol ○ results ○ method validation 	Y	
Drug Product [3.2.P] [Dosage Form]		
<input type="checkbox"/> description and composition	Y	
<input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity 	Y NA Y	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> batch formula	Y N	TBD by OBP
<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)	Y	Semi-finished syringe manufacturing in section 3.2.P. Prefilled syringe and pen injector assembly, packaging, and labeling in section 3.2.R. The adequacy of the information in 3.2.R is TBD by CDRH.
<input type="checkbox"/> controls of critical steps and intermediates	Y	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> ○ Filter validation 	Y Y	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <input type="radio"/> Component, container, closure depyrogenation and sterilization validation <input type="radio"/> Validation of aseptic processing (media simulations) <input type="radio"/> Environmental Monitoring Program <input type="radio"/> Lyophilizer validation <input type="radio"/> Other needed validation data (hold times) <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin) <input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities) <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> <input type="radio"/> specifications (vial, elastomer, drawings) <input type="radio"/> availability of DMF & LOAs <input type="radio"/> administration device(s) <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="radio"/> protocol <input type="radio"/> results <input type="radio"/> method validation 	<ul style="list-style-type: none"> Y Y Y NA Y Y N Y Y N Y Y 	<p align="right">(b) (4)</p>  <p>Some EM information provided in section 3.2.A instead of P.3.5. The sponsor will be asked to move this information to P.3.5.</p> <p>TBD by OBP</p> <p>TBD by OBP</p> <p>CCI method validation in section P.5.</p>
<p>Diluent (vials or filled syringes) [3.2P']</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <input type="radio"/> preservative effectiveness <input type="radio"/> container-closure integrity <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, 		<p>Not applicable. The DP is not supplied with a diluent.</p>

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<p>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 	<p align="center">Y N</p>	<p align="center">TBD by CDRH.</p>

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> other marketed chemicals (e.g. part of kit)	Y N	Not applicable.
Appendices for Biotech Products [3.2.A]		
<input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination 	Y	
<input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production 	Y N	Defer to OBP.
<input type="checkbox"/> novel excipients	Y N	Defer to OBP.
USA Regional Information [3.2.R]		
<input type="checkbox"/> executed batch records	Y	
<input type="checkbox"/> method validation package	Y	
<input type="checkbox"/> comparability protocols	Y	
Literature references and copies [3.3]	Y	

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

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

Examples of Filing Issues	Yes?	If not, justification, action & status
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to OBP.
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	Defer to OBP.
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y Y N Y	Summary. The reports will be requested. Defer to OBP.
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
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.

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/s/

COLLEEN THOMAS
11/04/2013

BO CHI
11/04/2013

PATRICIA F HUGHES TROOST
11/05/2013