CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125327Orig1s000

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date:	December 28, 2011
To:	Administrative File, STN 125327
From:	Lakshmi Rani Narasimhan, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement:	Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OC/OMPQ/DGMPA/BMAB
Subject:	Biological License Application (BLA)
US License:	# 1861
Applicant:	BTG International Inc.
Mfg Facility:	Cangene BioPharma Inc. (CBI), 1111 South Paca Street, Baltimore, MD 21230, USA (FEI # 1000512361)
Product:	Voraxaze™ (glucarpidase)
Dosage:	Sterile, powder for injection, for Intravenous administration. Contains 1000 units/vial
Indication:	For the (b) (4) reduction in toxic methotrexate (MTX) levels in patients receiving MTX who have toxic MTX levels due to impaired renal function.
Due Date:	January 17, 2012.

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective with the following post-market commitments:

1. Validate the integrity of Container Closure for the Voraxaze drug product using worst case crimping parameters (b) (4) for the capper. Validation information and summary data of the ingress test should be submitted in a CBE-0 by January 2013.

2. Revise the post approval stability program for microbiological testing. The sterility tests should be performed (b) (4) Alternatively, revise the stability program to include a container closure integrity testing of the finished product vials in lieu of sterility testing. Please report the revised post approval stability program in an annual report by January 2013.

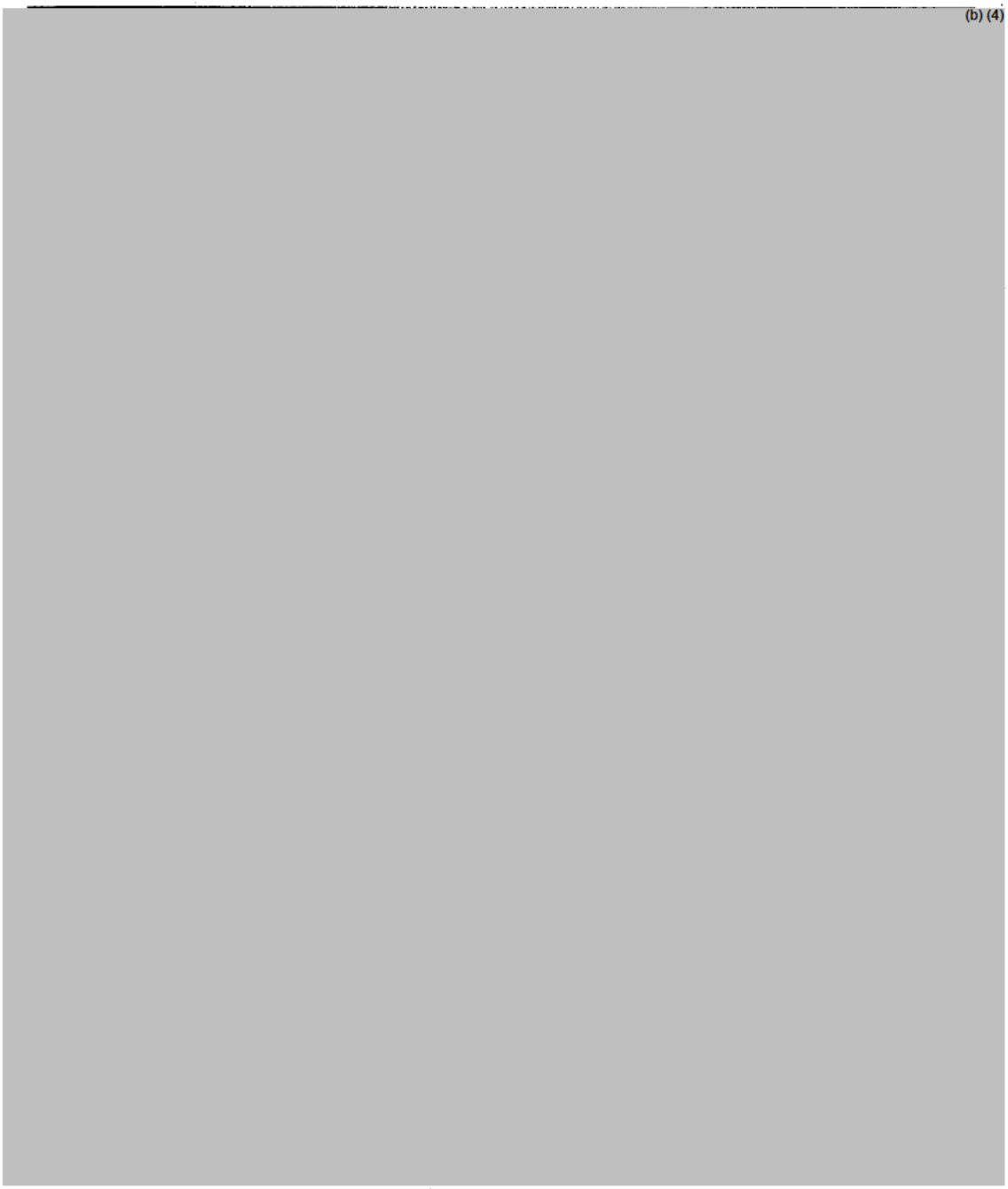
3. Provide information and data for low temperature worst case shipping validation study for finished drug product in a CBE-30 by June 2012.

SUMMARY: BTG International Inc. submitted a new biologics license application, STN 125327 to license Voraxaze™ (glucarpidase). This BLA was submitted in the rolling format, with Sequence 0004 containing Modules 2.3 and 3 submitted on 29 September 2010. This was followed by Sequence 0005 containing Modules 2.4, 2.6 and 4 on 16 December 2010, followed by Sequence 0006, submitted on 30 June 2011 containing Module 1, 2.2, 2.5, 2.7 and 5 and updates to Modules 2.3 and 3. The information request responses were submitted on 16 September 2011 in Sequence 0009, on 08 October 2011 in Sequence 0013, and on 12 December

2011 in Sequence 0017 were reviewed. The referenced INDs are 11557, 4663 and 11630, the last two INDs are held by the National Cancer Institute.

Glucarpidase is a recombinant enzyme produced by *Escherichia coli* (b) (4) through fermentation. Glucarpidase is a zinc-dependent exopeptidase enzyme with a molecular weight of approximately 83,000 Daltons. In patients with impaired renal function who are unable to clear MTX efficiently, treatment with glucarpidase provides an alternate route of MTX elimination. Glucarpidase has been shown to cleave MTX into inactive metabolites, 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA) and glutamate which are metabolized by the liver. Drug substance is manufactured by Eurogentec S.A. at Seraing, Belgium and drug product is filled and finished at Cangene BioPharma Inc. (CBI), Baltimore, Maryland, USA.

(b) (4)



32 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

(b) (4)

[redacted]

Conclusion

I The drug product section of this BLA was reviewed from sterility assurance perspective and is recommended for approval with the following post market commitments:

1. Validate the integrity of Container Closure for the Voraxaze drug product using worst case crimping parameters (b) (4) for the capper. Validation information and summary data of the ingress test should be submitted in a CBE-0 by January 2013.

2. Revise the post approval stability program for microbiological testing. The sterility tests should be performed (b) (4) Alternatively, revise the stability program to include a container closure integrity testing of the finished product vials in lieu of sterility testing. Please report the revised post approval stability program in an annual report by January 2013

3. Provide information and data for low temperature worst case shipping validation study for finished drug product in a CBE-30 by June 2012.

II The Analytical test results for the batch analyses and stability data should be reviewed by the OBP reviewer.

III. There are no follow-up inspectional items.

SIGNATURE/DISTRIBUTION LIST

Primary BMAB Reviewer: Lakshmi Rani Narasimhan, Ph.D. Date: 29 Dec '11

Concurring BMAB Acting Branch Chief: Patricia. F. Hughes, Ph.D Date: 12/29/2011

CC: Building 51, Hughes
Building 51, Narasimhan
Building 22, Laughner
Building 51, eCTD Files (STN 125327)

Archived File: S:\archive\BLA \125327\l25327.0.rev .mem.BLA.DP.12-29-11.doc

Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date: October 26, 2011

From: Lakshmi Rani Narasimhan, Ph.D., OC/OMPQ/DGMP/BMAB
Howard Anderson, Ph.D., OPS/OBP/DTP

To: BLA File, STN 125327/0 PFH Oct 26, 2011

Through: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OC/OMPQ/DGMP/BMAB

Subject: Biological License Application (BLA)

Applicant: BTG International Inc.

Facility: Cangene BioPharma Inc. (CBI), 1111 South Paca Street, Baltimore, MD 21230, USA (FEI # 1000512361)

Product: Voraxaze™ (glucarpidase)

Dosage: Sterile, powder for injection, for Intravenous administration. Contains 1000 units/vial

Indication: For the (b) (4) reduction in toxic methotrexate (MTX) levels in patients receiving MTX who have toxic MTX levels due to impaired renal function.

Waiver Recommendation
Based on the compliance history of the firm, the current GMP status, and the fact that Cangene BioPharma Inc. has been approved to manufacture multiple licensed products using the same manufacturing process, we recommend that the pre-approval inspection of the Cangene BioPharma Inc. drug product manufacturing facility in 1111 South Paca Street, Baltimore, MD 21230 USA (FEI: 1000512361) be waived for STN 125327/0 (submission dated 18 July 2011).

Clearance Routing

Acting for ~~Barry Rothman~~, David Doleski CONCUR/ NONCONCUR DATE 12/15/2011
Director (Acting), Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality, Office of Compliance, CDER

for Amy Rosenberg, M.D. CONCUR/NONCONCUR DATE 10-11-1-2011
Director, Division of Therapeutic Proteins, Office of Biotechnology Products,
Office of Pharmaceutical Science, CDER

Summary

BLA 125327/0 is for glucarpidase (proposed name: Voraxaze™) which provides for the elimination of MTX in patients with impaired renal function and who are unable to clear MTX efficiently. Glucarpidase drug product is supplied as a sterile powder for injection, for intravenous administration in 3 mL USP Type 1 glass vials. Each vial contains 1000 Units of glucarpidase, for injection after reconstitution with 1 mL sterile normal saline. The normal saline is not included in the pack. Voraxaze is supplied in a 1 vial pack size.

The drug substance, glucarpidase is a recombinant enzyme produced by fermentation from a recombinant strain of *Escherichia coli* (b) (4) (b) (4) (b) (4)

Facility Information
All activities related to Voraxaze manufacture take place in (b) (4) at Cangene bioPharma Inc. (CBI), Baltimore, Maryland, USA which is a multi-product contract manufacturing for (b) (4) filled products in liquid or lyophilized form. (b) (4) (b) (4) (b) (4)

The process includes: (b) (4)

Supporting Information

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*
   a. Cangene bioPharma Inc. (CBI), Baltimore, Maryland, USA (FEI # 1000512361) will manufacture Voraxaze product which is the subject of BLA 125327 that is currently under review at the Agency.
   b. CBI is approved for manufacturing licensed biological products such as (b) (4) (b) (4)

2. *FDA has not inspected the establishment in the last 2 years.*
   FDA has inspected the establishment several times in the past 2 years.

(b) (4)

Inspection conclusions
Inspected by BLT-DO. The following profile classes were covered: AEV, TRP, SVP, SNI, SLQ, SVL, SVS, SVT, and FSP. The inspection was classified VAI and the firm has acceptable GMP status.
Inspected by BLT-DO. The following profile classes were covered: AEV, TRP, SVP, SVL, SVS, SVT, and FSP. The inspection was classified VAI and final GMP status was acceptable.
Inspected by Team Biologics and was classified VAI and final GMP status was acceptable.
Inspected by BLT-DO and was classified NAI. No FDA 483 was issued.

3. The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.
The site has acceptable compliance status.

(b) (4)

5. The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment. Point to consider:
The manufacturing process for this BLA is substantially equivalent to other parenteral products manufactured in the same facility.

Signed:

Lakshmi Rani Narasimhan, Ph.D
Microbiologist
OC/OMPQ/DGMP/BMAB
Lakshmi Rani. O Date 26 Oct'11

Howard Anderson, Ph.D
Biologist
OPS/OBP/DTP
Date Oct 27, 2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: 20 Dec 2011
To: Administrative File, STN 125327/0
From: Mary E. Farbman, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OC/OMPQ/DGMPA/BMAB
Subject: New BLA
US License: 1861
Applicant: BTG International Inc.
Mfg Facility: [for drug substance]: Eurogentec S.A., Seraing, Belgium (FEI 3003323169)
Product: Voraxaze® (glucarpidase)
Dosage: 50 units/kg body weight; supplied as sterile lyophilized powder with 1000 units/vial and given as a single intravenous administration
Indication: elimination of methotrexate
Due Date: 17 Jan 2012

Recommendation for Approvability

The drug substance section (3.2.S) of the BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments:

1. Complete the qualification of the bioburden assay using two additional batches of drug substance. The final qualification report should be submitted as a product correspondence by a date to be determined.
2. Submit a shipping validation report to support shipping conditions of drug substance to the drug product manufacturing site. The report should be submitted as a product correspondence by March 2012.

Summary

BTG International has submitted a BLA for Voraxaze® (glucarpidase), an enzyme to be used as an antidote to methotrexate toxicity. Glucarpidase, the active agent in Voraxaze, is a recombinantly produced, zinc-dependent homodimer enzyme capable of hydrolysis of the carboxy-terminal glutamate residue of folic acid and folic acid analogues, including

methotrexate. The resulting products of glucarpidase-dependent methotrexate hydrolysis are further metabolized by the liver.

Glucarpidase drug substance is manufactured at Eurogentec S.A., in Seraing, Belgium. The protein is recombinantly expressed in *E. coli* cells and is purified using standard biotechnology methods. This review covers the microbiology product quality of the glucarpidase drug substance as described in the following BLA amendments:

- Amendment 125327/0/4 (eCTD #0004, submitted 29 Sep 2010): initial CMC/Module 3 submission
- Amendment 125327/0/7 (eCTD #0007, submitted 18 Jul 2011): statement that all manufacturing sites are ready for inspection
- Amendment 125327/0/9 (eCTD #0009, submitted 16 Sep 2011): shipping validation protocol for shipment of drug substance to drug product manufacturing site
- Amendment 125327/0/13 (eCTD #0013, submitted 07 Nov 2011): response to microbiology product quality Information Request sent to firm on 04 Oct 2011
- Amendment 125327/0/17 (eCTD #0017, submitted 08 Dec 2011): response to microbiology product quality Information Request sent to firm on 05 Dec 2011

A pre-license inspection of Eurogentec S.A. was conducted in support of the BLA. The preliminary recommendation for the inspection was VAI.

The drug substance section (3.2.S) of the BLA, as amended, is recommended for approval from a microbiology product quality perspective. The following two post-marketing commitments are proposed:

- Complete the qualification of the bioburden assay using two additional batches of drug substance. The final qualification report should be submitted as a product correspondence by a date to be determined.
- Submit a shipping validation report to support shipping conditions of drug substance to the drug product manufacturing site. The report should be submitted as a product correspondence by March 2012.

(b) (4)

15 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

SIGNATURES/DISTRIBUTION LIST

Primary BMAB Reviewer: Mary E. Farbman, Ph.D. mef Date: 20dec11
Concurring BMAB Acting Branch Chief: Patricia Hughes, Ph.D. PH Date: 12/5/2012

CC: OC/DMPQ/BMT/Building 51, Farbman
OC/DMPQ/BMT/Building 51, Hughes
OC/OODP/DBOP/Building 22, Laughner
OC/DMPQ/BMT/Building 51, eCTD Files (STN 125327)

Archived File: S:\archive\BLA\125327\125327.0.rev.mem.BLA.DS.12-20-11.doc

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

BLA/NDA Number: STN 125327/0

Applicant: BTG International Inc.

Stamp Date:

Established/Proper Name: Glucarpidase

BLA/NDA Type: Priority review

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 ❑ including list of all establishment sites and their registration numbers	Y	FEI number for drug substance manufacturing site, Eurogentec S.A., is not submitted in the BLA. However, the site is registered, and the amendment filed as eCTD #0007 states that the site is ready for inspection.
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y N Y Y N Y N Y N Y N Y N Y N Y N Y N Y N	

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: ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components	Y Y Y Y Y Y Y Y	

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)		
Companion application received if a shared or divided manufacturing arrangement	Y	

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] ❑ Drug Substance ❑ Drug Product ❑ Facilities and Equipment ❑ Adventitious Agents Safety Evaluation ❑ Novel Excipients ❑ Executed Batch Records ❑ Method Validation Package ❑ Comparability Protocols	Y Y Y Y TBD by OBP/DTP TBD by OBP/DTP Y Y N	Comparability protocols: not applicable

CTD Module 3 Contents	Present ?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S] ❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ description of manufacturing process and process control o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping ❑ control of materials o raw materials and reagents o biological source and starting materials	Y Y Y TBD by OBP/DTP	Shipping validation of DS to site of DP manufacture was not submitted in the BLA. BLA states that validation study is in progress.

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

CTD Module 3 Contents	Present ?	If not, justification, action & status
○ cell substrate: source, history, and generation ○ cell banking system, characterization, and testing		
❑ control of critical steps and intermediates ○ justification of specifications ○ stability	Y	
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance	TBD by OBP/D	
❑ control of drug substance ○ specifications ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses	TP Y Y Y	
❑ reference standards	Y	
❑ container closure system	TBD by OBP/D	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	TP Y Y	
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development ○ preservative effectiveness ○ container-closure integrity	Y N Y	NA. Insufficient information- IR was sent out on 17 Aug 11 and response was received on 29 Aug 11.
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	

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

CTD Module 3 Contents	Present ?		If not, justification, action & status
❑ batch formula	Y	N	OBP review.
❑ 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		
❑ controls of critical steps and intermediates	Y		Microbial controls.
❑ process validation including aseptic processing & sterility assurance:	Y		Microbial control and sterility assurance.
o Filter validation	Y		Insufficient information-IR was sent out on 17 Aug 11 and response was received on 29 Aug 11.
o Component, container, closure depyrogenation and sterilization validation	Y		No information was provided on containers, closure and equipment in contact with sterile product, (b) (4), and environmental monitoring-IR was sent out on 17 Aug 11 and response was received on 29 Aug11 and 02 Sep 11.
o Validation of aseptic processing (media simulations)	Y		
o Environmental Monitoring Program	Y		
o Lyophilizer validation	Y		
o Other needed validation data (hold times)		Y	Shipping Validation: Insufficient information- IR was sent out on 17 Aug 11 and response was received on 29 Aug 11. (b) (4) testing and method qualification is not included. IR was sent out on 17 Aug 11 and response was received on 29 Aug 11.
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	N	OBP review
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y		Sterility and endotoxin

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

CTD Module 3 Contents	Present ?	If not, justification, action & status
❑ reference standards or materials	Y N	NA- OBP review
❑ container closure system [3.2.P.7]	Y	OBP lead
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs		
o administration device(s)		
❑ stability	Y	
❑ summary		Sterility and endotoxin
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
o method validation		
Diluent (vials or filled syringes) [3.2P']	Y N	NA- No diluent included
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
o preservative effectiveness		
o container-closure integrity	Y N Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula		
❑ 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 N Y N Y N	
❑ controls of critical steps and intermediates		
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program	Y N	

CTD Module 3 Contents	Present ?	If not, justification, action & status
○ Lyophilizer sterilization validation ○ Other needed validation data (hold times)	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N Y N	
❑ reference standards		
❑ container closure system ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results		
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y N Y N	NA
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment ○ 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	
❑ adventitious agents safety evaluation (viral and non-viral) e.g.:	TBD by OBP/D	

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

CTD Module 3 Contents	Present ?	If not, justification, action & status
○ 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 ❑ novel excipients	TP TBD by OBP/D TP	
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y Y N	 OBP lead. Endotoxin and sterility. NA
Literature references and copies [3.3]	Y	OBP review

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	NA
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	NA
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	NA
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	Microbial product quality tests.

PRODUCT QUALITY (Biotechnology)

FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
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: ❑ LAL instead of rabbit pyrogen	N	Comparison to of LAL to rabbit pyrogen is not included. Waiver letter will be requested.
❑ mycoplasma	Y N	OBP review.
❑ sterility	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 N	NA
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.

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

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

Mary E Farbman Lakshmi Rani N 06Sep11 06Sep11

Product Quality Reviewer(s) Date

07Sept11

Branch Chief/Team Leader/Supervisor Date

9/7/2011

Division Director Date