

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125431Orig1s000

CHEMISTRY REVIEW(S)

OBP CMC Review Data Sheet

- BLA#:** STN 125431
Applicant: GLAXOSMITHKLINE LLC / 1727

Product: ALBIGLUTIDE

Indication: Type II diabetes

Proprietary Name: EPERZAN; TANZEUM
- APPLICATION INFORMATION:**
Application Number: 125431\0\58, 59 & 60

eCTD Sequence Number: 0057, 0058 and 60

CBER Receipt Date: STN 58-28-Mar-2014, STN 59- 8-April-2014, STN 60- 9-Apr-14
- REVIEW DATE: STN 58 March 31, 2014**
59 April 8 2014
60 April 9, 2014
- PRIMARY REVIEW TEAM:**
Medical Officer: Kaveeta Vasisht

Pharm/Tox: Ronald Wange

Product Quality Team: João Pedras-Vasconcelos, Arulvathani Arudchandran, Montserrat Puig/ Susan Kirshner/ Emanuela Lacana

Immunogenicity: João Pedras-Vasconcelos/Susan Kirshner

BMT or Facilities: Lakshmi Narasimhan, Bo Chi/ Patricia Hughes

Clinical Pharmacology: Suryanarayana Sista

Statistics: Bo Li

OBP Labeling: NA

RPM: Ray Chiang
- MAJOR 21st Century Review DEADLINES**

Filing Meeting Feb 27, 2013

Mid-Cycle Meeting: June 26, 2013

CMC Extension granted: July 30, 2013

Wrap-Up Meeting: Feb 26, 2013

Primary CMC Review Due: Dec 1, 2013

Secondary Review Due: Dec 17, 2013

CDTL Memo Due: March 10, 2014

PDUFA Action Date: April 15, 2014

Submission:

Albiglutide (GSK716155/TANZEUM™) is a 73 kDa recombinant human glucagon-like peptide 1 (GLP-1)-human serum albumin (HSA) fusion protein produced through (b) (4) of a genetically modified strain of *Saccharomyces cerevisiae*. It is being proposed for the treatment of type 2 diabetes mellitus (T2DM) by GlaxoSmithKline LLC (GSK) as a long-lived analogue of native GLP-1. The primary quality review for this BLA was completed and loaded into DARRTS on December 17, 2013 with a recommendation for approval.

On March 21st, 2014 GSK contacted Dr. Patricia Hughes, the BMAB team leader, by telephone to report a hitherto unknown issue concerning (b) (4)

(b) (4) This issue was first discovered in Dec 2013 not with albiglutide, (b) (4)

(b) (4) The investigation was subsequently extended to albiglutide once it was realized that (b) (4)

(b) (4) Once their investigation reached an advanced state, the sponsor contacted the FDA by telephone. Following an internal discussion between DTP and BMAB the following information request was sent to the sponsor on March 25, which was followed by a teleconference.

BLA 125431 Albiglutide GSK (b) (4) requests for information and questions to be conveyed to the sponsor

1. A copy of all the investigation reports related to the (b) (4)

21 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

(b) (4)



(b) (4)



Comment to the file:

The sponsor agreed to and provided tentative completion dates for these new PMCs (#1-Jan, 2015 and #2-June 2015). These dates are acceptable, as are the dates proposed for the final report submission for the previous CMC PMCs-PMC #5 (an UPLC assay for release and stability- May 2015); and PMC #6 (FcRn binding assay for monitoring HSA portion of molecule-Aug 2015).

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/s/

JOAO A PEDRAS VASCONCEL

04/11/2014

(b) (4) issues have been addressed and initial recommendation for approval remains active.

SUSAN L KIRSHNER

04/11/2014

BLA 125431: LCM Discussion:

Primary reviewer : Arulvathani Arudchandran, Ph.D., DTP.

Secondary reviewer : Susan Kirshner, Ph.D. DTP

Comment to the Sponsor:

You proposed to discontinue (b) (4) upon completion of the Registration Stability a (b) (4) ms. The agency accepts your proposal. However, the agency recommends you to use the (b) (4) method to assess the (b) (4) (b) (4) in the drug product as a characterization test.

Review:

The following review is for the two PMC requests discussed for the DP during the LCM with the sponsor.

(b) (4)

Response from Sponsor:

(b) (4)

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/s/

JOAO A PEDRAS VASCONCEL
02/20/2014

ARULVATHAN P ARUDCHANDRAN
02/20/2014

SUSAN L KIRSHNER
02/20/2014

OBP CMC Review Data Sheet

1. **BLA#:** STN 125431
2. **REVIEW DATE:** Feb 14, 2014
3. **PRIMARY REVIEW TEAM:**
Medical Officer: Kaveeta Vasisht
Pharm/Tox: Ronald Wange
Product Quality Team: João Pedras-Vasconcelos, Arulvathani Arudchandran, Montserrat Puig/ Susan Kirshner/ Emanuela Lacana
Immunogenicity: João Pedras-Vasconcelos/Susan Kirshner
BMT or Facilities: Lakshmi Narasimhan Bo Chi/ Patricia Hughes
Clinical Pharmacology: Suryanarayana Sista
Statistics: Bo Li
OBP Labeling: NA
RPM: Ray Chiang
4. **MAJOR 21st Century Review DEADLINES**
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5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

The immunogenicity assays for detection of anti-albiglutide antibodies (Ab; screening/confirmatory and neutralizing), anti-HSA antibodies (screening/confirmatory), and anti- hGLP-1 (screening, confirmatory, titration, and neutralizing) were previously reviewed by the division under IND 65177 (GSK716155/Albiglutide), and were deemed suitable for their intended purpose. The anti-albiglutide IgE ab ELISA was reviewed by ONDQA under IND 65177 during their tenure of the product, and they had deemed it suitable for its intended purpose.

The sponsor resubmitted the following reviewed reports:

2010N103951 Validation Report of an Improved Method for screening, confirmation and titration of anti-GLP1 antibodies in human serum

2010N108159 Method for the detection of anti-human albumin antibodies in human serum

2010N113641 Validation report of a method for the detection of anti-human albumin antibodies in human serum

2010N117330 ELISA for screening confirmation and titration of anti-Glucagon antibodies

2010N117331 ELISA for screening confirmation and titration of anti-GLP-1 antibodies

2011N117983 Neutralizing Antibody assay for GSK716155 in human serum

2011N117984 Method Qualification report for Neutralizing Antibody assay for GSK716155 in human serum

2011N118005 Validation for the detection of anti-GSK716155 antibodies in human serum
2011N1125834 Assay Qualification report of a GLP-1 Neutralizing Antibody assay in human serum
2011N1125835 Neutralizing Antibody assay for GLP-1 in human serum
2011N129539 Validation for the detection of anti-GSK716155 IgE antibodies in human serum
2011N122140 Within-Study analytical performance data for the determination of GSK716155 in human plasma- a dose finding study of GSK716155 vs Placebo in human plasma for GSK study number GLP110932

(b) (4)

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Proposed Immunogenicity label:

Immunogenicity:

(b) (4)

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to albiglutide cannot be directly compared with the incidence of antibodies of other products.

Comment to the file:

In the immunogenicity label, the sponsor chose to include only data from 2098 patients from 7 phase III studies, where 116 subjects (9 subjects with pre-existing ADA, and 107 treatment-emergent subjects) tested positive for ADA, leading to an immunogenicity rate of 5.5% (116/2098). This is slightly higher than the overall rate and is acceptable. The opening boilerplate sentence from the labeling tool will be added to the label. At the time this review was finalized labeling discussions with the sponsor were ongoing.

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/s/

JOAO A PEDRAS VASCONCEL
02/14/2014

BLA STN 125431

**Product USAN name
TANZEUN (albiglutide)**

**Manufacturer
Glaxo Smith Kline**

**Reviewer: João A. Pedras-Vasconcelos
Reviewer: Arulvathani Arudchandran
Reviewer: Montserrat Puig
Secondary Reviewer: Susan Kirshner
Tertiary Reviewer: Emanuela Lacana
Division of Therapeutic Proteins**

OBP CMC Review Data Sheet

1. **BLA#:** STN 125431
2. **REVIEW DATE:**
3. **PRIMARY REVIEW TEAM:**
Medical Officer: Kaveeta Vasisht
Pharm/Tox: Ronald Wange
Product Quality Team: João Pedras-Vasconcelos, Arulvathani Arudchandran, Montserrat Puig/
Susan Kirshner/ Emanuela Lacana
Immunogenicity: João Pedras-Vasconcelos/Susan Kirshner
BMT or Facilities: Lakshmi Narasimhan Bo Chi/ Patricia Hughes
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5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Information Request 1-DS, DP, and CC	5/10/2013
PLI close out communication	8/23/2013

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
Primary submission	1/14/2013	yes
IR- sponsor response	6/14/2013	yes
Post-PLI IR	9/2/2013	yes
Amend 36- Specifications and justification of specifications updates	10/8/2013	yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

- a. Proprietary Name: TANZEUM
- b. Trade Name: TANZEUM
- c. Non-Proprietary/USAN: Albiglutide
- d. CAS name: 782500-75-8
- e. Common name: Albiglutide
- f. INN Name: NA
- g. Compendial Name: NA
- h. OBP systematic name: FUS:ALBUMIN HUMAN; RPROT P01275 (GLP1_HUMAN) [GK716155]
- i. Other Names: GSK716155 (company code)
 recombinant human glucagon-like peptide (GLP-1) human albumin fusion protein
 Albiglutidum (Latin)
 Albiglutida (Spanish)
 Albugon (former company name)

- 8. **PHARMACOLOGICAL CATEGORY:** GLP-1 receptor agonist, incretin fusion protein
- 9. **DOSAGE FORM:** For injection in a single-dose Pen
- 10. **STRENGTH/POTENCY:** 30 mg or 50 mg
- 11. **ROUTE OF ADMINISTRATION:** Intramuscular
- 12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCE D	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			yes	Reviewed by CDRH
			yes	Reviewed by CDRH
			yes	
			yes	Reviewed by Montserrat Puig; found to be adequate.
			yes	Reviewed by CDRH
			yes	Reviewed by CDRH
			yes	Reviewed by CDRH
			yes	Reviewed by CDRH
			yes	510 (k) file reviewed by CDRH

13. INSPECTIONAL ACTIVITIES

A pre-license inspection of the facility for the manufacture of albiglutide drug substance was conducted at GlaxoSmithKline (GSK), LLC., (b) (4), 893 River Road, Conshohocken, PA 19428 on Aug 19-23/2013.

14. CONSULTS REQUESTED BY OBP- CDRH DP DEVICE AND PATIENT FACTOR STUDIES

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment / Risk Management
x	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS - None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Susan Kirshner, Ph. D Review Chief, Division of Therapeutic Proteins Team Leader	
Emanuela Lacana, Ph. D. Tertiary Reviewer, Division of Therapeutic Proteins	
João Antonio Pedras-Vasconcelos, Ph.D. Arulvathani Arudchandran, Ph. D. Montserrat Puig, Ph.D. Primary Reviewer (s) Division of Therapeutic Proteins	

B. CC Block

Recipient	Date
Raymond Chiang	

Clinical Division BLA RPM	
Division of Therapeutic Proteins File/BLA STN 125431	

SUMMARY OF QUALITY ASSESSMENTS

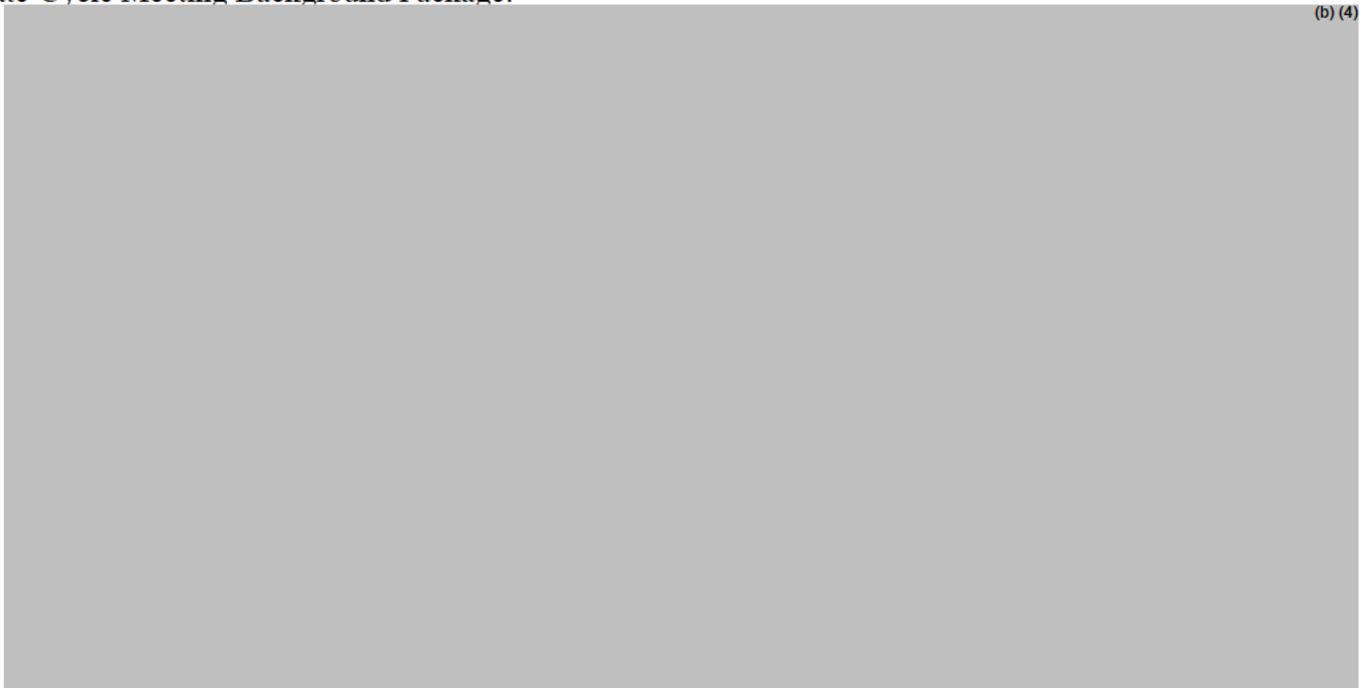
I. Primary Reviewer Summary Recommendation

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA STN 125431 for Tanzeum (Albiglutide) manufactured by GlaxoSmithKlein LLC, pending resolution of the review issues described below in section II. The data submitted in this application are adequate to support the conclusion that the manufacture of Eperzan is well controlled, and leads to a product that is pure and potent.

The sponsor should provide response to our pending information requests. The review of these items will be an addendum to this review and based on the adequacy of the responses, the resulting issues may become additional PMCs.

II. List Of Deficiencies To Be Communicated

We will communicate the following review issues to the sponsor in the Discipline Review Letter or the Late-Cycle Meeting Background Package:



- B. In amendment 36, you recently submitted new specifications and justifications of specifications for drug substance (attachments 1 and 2) and drug product (attachments 3 and 4) but failed to update the appropriate sections of the eCTD. Please update Sections 3.2.S.4.1, 3.2.S.4.5, 3.2.P.5.1, and 3.2.P.5.6 as appropriate.
- C. If you would like an (b) (4) dating period for DS and DP, please provide (b) (4) stability update for process 3 registration lots of drug substance and drug product to the file.

III. List Of Post-Marketing Commitments/Requirement

The sponsor will commit to the following Post-Marketing Commitments:

1. To develop, validate and implement an ultra-performance liquid chromatography (UPLC) analytical method to assess purity for release and stability of drug substance and drug product.
2. To develop, validate, and implement an FcRN binding assay to monitor functionality of human albumin portion of drug substance and drug product for release and stability

(b) (4)

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim Of Categorical Exclusion

A categorical exclusion is requested by GlaxoSmithKline, LLC under 21 CFR Part 25.31(c). As stated in 21 CFR Part 25.31(c), action on an BLA or BLA supplement is categorically excluded from environmental assessment requirements if the action is for a substance which occurs naturally in the environment, when the action does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

V. Primary Container Labeling Review

The primary container labeling review was performed by DMEPA.

VI. Review Of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

An immunogenicity review was performed by João Pedras-Vasconcelos and will be added to the file as a separate document.

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/s/

JOAO A PEDRAS VASCONCEL
12/16/2013
Primary CMC review for Tanzeun (albiglutide)

MONTSERRAT PUIG
12/17/2013

ARULVATHAN P ARUDCHANDRAN
12/17/2013

SUSAN L KIRSHNER
12/17/2013

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

BLA/NDA Number:

Applicant:

Stamp Date:

STN 125431/0

GlaxoSmithKline LLC

Established/Proper Name:

BLA/NDA Type:

albiglutide/

Standard review

Eperzan(proposed)

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	
Comprehensive Table of Contents	Y N	Not required
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	Defer to OND and OBP.

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 shared or divided manufacturing	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
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	Not required.
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	Defer to OBP
<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 N	
<input type="checkbox"/> Novel Excipients	Y N	
<input type="checkbox"/> Executed Batch Records	Y N	
<input type="checkbox"/> Method Validation Package	N	
<input type="checkbox"/> Comparability Protocols	Y	

CTD Module 3 Contents	Present ?	If not, justification, action & status
Module Table of Contents [3.1]	N	Not required.
Drug Substance [3.2.S]	Y	Defer to OBP
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> 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="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> control of materials	Y N	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and	Y	(b) (4)

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

CTD Module 3 Contents	Present ?	If not, justification, action & status
effectiveness		
o container-closure integrity	Y	
□ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
□ batch formula	Y	N
□ 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	Not applicable.
□ controls of critical steps and intermediates	Y	
□ process validation including aseptic processing & sterility assurance:	Y	
o Filter validation	Y	
o Component, container, closure depyrogenation and sterilization validation	Y	
o Validation of aseptic processing (media simulations)	Y	
o Environmental Monitoring Program	Y	
o Lyophilizer sterilization validation	Y	N
o Other needed validation data (hold times)	Y	
□ 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	
□ reference standards	Y	N
□ container closure system	Y	Not applicable.
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs		
□ stability	Y	
□ summary		

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

CTD Module 3 Contents	Present ?	If not, justification, action & status
<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 		
Other components to be marketed (full description and supporting data, as listed above): <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit)	 Y Y N	 Not applicable.
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, sterilization and storage <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 Y N Y N	 Defer to OBP Defer to OBP
USA Regional Information [3.2.R] <input type="checkbox"/> executed batch records <input type="checkbox"/> method validation package <input type="checkbox"/> comparability protocols	 Y N Y N Y	 Defer to OBP Provided in 3.2.S and 3.2.P. Defer to OBP
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug	Y	

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

Examples of Filing Issues	Yes?	If not, justification, action & status
substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)		
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.
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	
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	Y	
<input type="checkbox"/> mycoplasma	Y N	Defer to OBP
<input type="checkbox"/> 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	
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	

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

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes ~~No~~

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/

BO CHI
03/12/2013

LAKSHMI RANI NARASIMHAN
03/12/2013

PATRICIA F HUGHES TROOST
03/12/2013

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

BLA/NDA Number:

Applicant: GSK

Stamp Date: 1/14/13

125431

Established/Proper Name: BLA/NDA Type: Standard

Albiglutide (EPARZAN)

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

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	<u>Y</u> N	
Form 356h completed	<u>Y</u> N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<u>Y</u> N	
Comprehensive Table of Contents	<u>Y</u> N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	<u>Y</u> N	
Labeling:	<u>Y</u> N	
<input type="checkbox"/> PI –non-annotated	<u>Y</u> N	
<input type="checkbox"/> PI –annotated	<u>Y</u> N	
<input type="checkbox"/> PI (electronic)	<u>Y</u> N	
<input type="checkbox"/> Medication Guide	<u>Y</u> N	
<input type="checkbox"/> Patient Insert	<u>Y</u> N	
<input type="checkbox"/> package and container	<u>Y</u> N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	<u>Y</u> N	
<input type="checkbox"/> proprietary name (for review)	<u>Y</u> 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:	<u>Y</u> N	
<input type="checkbox"/> legible	<u>Y</u> N	
<input type="checkbox"/> English (or translated into English)	<u>Y</u> N	
<input type="checkbox"/> compatible file formats	<u>Y</u> N	
<input type="checkbox"/> navigable hyper-links	<u>Y</u> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<u>Y</u> N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<u>Y</u> N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<u>Y</u> N	
Companion application received if a shared or divided manufacturing arrangement	Y <u>N</u>	NA

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

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

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

**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"> plan, results, analysis, and conclusions) <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="checkbox"/> specifications <input type="checkbox"/> justification of specs. <input type="checkbox"/> analytical procedures <input type="checkbox"/> analytical method validation <input type="checkbox"/> batch analyses <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <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 <input type="checkbox"/> method validation 	<ul style="list-style-type: none"> <u>Y</u> N 	
<p>Drug Product [3.2.P] [Dosage Form]</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <input type="checkbox"/> preservative effectiveness <input type="checkbox"/> 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, 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"> <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation and sterilization 	<ul style="list-style-type: none"> <u>Y</u> N 	

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

Examples of Filing Issues	Yes?	If not, justification, action & status
clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection	<u>Y</u> N	Timing of inspection?
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.	<u>Y</u> 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 that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	<u>Y</u> N <u>Y</u> N <u>Y</u> N	Not required (cell substrate not susceptible)
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	<u>Y</u> N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	<u>Y</u> N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	<u>Y</u> N	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?

Yes No

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

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 major potential review issue identified so far.

João A. Pedras-Vasconcelos Arulvathani Arudchandran Montserrat Puig	signed electronically
Product Quality Reviewer(s)	Date
Susan Kirshner	signed electronically
Branch Chief/ <u>Team Leader</u> /Supervisor	Date
Amy Rosenberg	signed electronically
Division Director	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOAO A PEDRAS VASCONCEL
02/26/2013
BLA 125431 Filling memo

SUSAN L KIRSHNER
02/28/2013

AMY S ROSENBERG
02/28/2013