CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125431Orig1s000

CHEMISTRY REVIEW(S)

First Approval for Indication

Recommendation: Approval

BLA 125431
Review 1
Review Date April 13, 2014

Drug Name/Dosage Form	**Tanzeun/For injection**
Strength/Potency	**30 mg or 50 mg**
Route of Administration	(b) (4)
Indication	**Improve glycemic control in Type 2 diabetes as an adjunct to diet and exercise**
Rx/OTC Dispensed	**Rx**
Applicant/Sponsor	**Glaxo Smith Kline**
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	Review completed
Original Submission	1/14/2013	Yes
Amendment 19	6/14/2013	Yes
Amendment 33	9/2/2013	Yes
Amendment 36	8/19/2013	Yes
Amendment 58	3/28/2014	Yes
Amendment 59	4/08/2014	Yes
Amendment 60	4/9/2014	Yes

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	**J Pedras Vasoconcelos, M Puig**	**DTP**
Drug Product	**A Arudchandran, M Puig**	**DTP**
Immunogenicity	**J Pedras Vasconcelos**	**DTP**
Labeling	**J Pedras Vasconcelos**	**DTP, DMEPA**
Facility and Microbiology	**L Narasimhan, B Chi, P Hughes**	**BMAB**
Secondary Reviewer	**S Kirshner**	**DTP**
Tertiary Reviewer	**Amy Rosenberg**	**DTP**

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Medical Officer	**K Vasisht**	**ODE II/DMEP**
Pharm/Tox	**R Wange**	**ODE II/DMEP**
Clinical Pharmacology	**S Sista**	**OCP/DCPII**
Statistics	**B Li**	**OB/DBVII**
RPM	**R Chiang**	**ODE II/DMEP**

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Reviewed by CDRH		Adequate
				3	Reviewed by CDRH		Adequate
				3			Adequate
				1	Reviewed by Montserrat Puig; found to be adequate.		Adequate
				3	Reviewed by CDRH		Adequate
				3	Reviewed by CDRH		Adequate
				3	Reviewed by CDRH		Adequate
				3	Reviewed by CDRH		Adequate
				3	510 (k) file reviewed		Adequate

					by CDRH		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Reviewed previously and no revision since last review

3 – Sufficient information in application

4 – Authority to reference not granted

5 – DMF not available

6 – Other (explain under "Comments")

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
CDRH – Drug product dual chamber cartridge and pen injector	3/22/2013	Completed	Adequate	Keith Marin, Lana Shiu
CDRH – Human factors study	3/7/2013	Completed	Adequate	QuynhNhu Nguyen

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125431 for Tanzeum manufactured by Glaxo Smith Kline. The data submitted in this application are adequate to support the conclusion that the manufacture of Tanzeum is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. Action letter language

- Manufacturing location:
  - Drug substance – GlaxoSmithKline LLC in Conshohocken, Pennsylvania
  - Drug product – at (b) (4)
- Fill sized and dosage form – 30 mg or 50 mg in a single-dose pen for injection
- Dating period:
  - Drug product – 12 months at 2 - 8ºC; an excursion of up to 30 days at 30ºC is allowed
  - Drug substance – (b) (4)
  - Stability option:
    We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
  - Yes
  - Rationale if exempted – Tanzeum is exempted from lot release because it is a specified product per 601.2a.

c. Benefit/Risk Considerations

Tanzeum is indicated to improve glycemic control as an adjunct to diet and exercise in patients with type 2 diabetes. It has not been studied with prandial insulin and is not indicated for the treatment of type 1 diabetes.

(b) (4)

(b) (4) have been in use since 2007. Therefore there is extensive clinical experience with Tanzeum in these containers.

(b) (4) Therefore, the dating period of albiglutide drug substance is currently limited to (b) (4). Confirmatory stability studies with drug substance stored in (b) (4) will be performed post-marketing. This is acceptable because, as noted above, the (b) (4) are not expected to impact stability by (b) (4). The sponsor also has a post-marketing commitment to implement use of (b) (4)

The Tanzeum manufacturing process is otherwise well controlled. There are two post-marketing commitments to improve drug product release testing. Tanzeum is a fusion protein comprised of two tandem repeats of GLP1 fused to human serum albumin (HSA). There is evidence that HSA increases the in vivo half-life of Tanzeum in part via a pathway that rescues endocytosed albiglutide from being degraded in lysosomes. This occurs because in the acidic endosomal environment the HSA portion of albiglutide binds to the neonatal Fc receptor (FcRn) on the endosome membrane. Rather than entering the lysosome, FcRn bound albiglutide is recycled back to the cell surface where it is released from the FcRn when the complex encounters neutral extracellular pH. (b) (4) However, as the HSA domain is large and other structural changes may impact its role in pharmacokinetics, it was agreed that albiglutide-FcRn binding should be directly monitored at release to provide increased assurance that the product will function as expected. To this end there is a post marketing commitment to develop and validate an FcRn binding assay.

There is also a post-marketing commitment to implement an ultra-performance liquid chromatography method for improved purity release testing. The current control strategy for release and stability of drug substance and drug product is adequate to monitor product quality and consistency of manufacturing. However, this improved method will provide greater measurement accuracy and better assurance of consistent product quality over time.

Tanzeum product quality and manufacturing risks are well managed and low. Therefore we recommend approval of this product with the four post-marketing commitments described below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments

a. 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.

b. To develop, validate, and implement a neonatal Fc receptor binding assay to monitor functionality of human albumin portion of drug substance and drug product for release and stability.

c. To perform a bulk drug substance stability study using samples stored for the desired shelf life in the [redacted] (b) (4). Stability testing should be performed on drug substance aliquots removed [redacted] (b) (4)

d. To implement CAPAs to establish [redacted] (b) (4) for bulk drug substance

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

The table below provides a summary of critical quality attributes identification and risk management. For the purposes of this table, critical quality attributes are limited to attributes intrinsic to the active pharmaceutical ingredient. Identification and risk management of process related impurities and general drug substance or drug product attributes are described in separate risk tables in sections B, Drug Substance Quality Summary, and C, Drug Product Quality Summary. Product variants are product variants that are fully active, or close to fully active. Product impurities are product variants that are inactive or have greatly reduced activity.

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/s/

SUSAN L KIRSHNER
04/18/2014

AMY S ROSENBERG
04/19/2014

OBP CMC Review Data Sheet

1. **BLA#:** STN 125431
Applicant: GLAXOSMITHKLINE LLC / 1727

Product: ALBIGLUTIDE

Indication: Type II diabetes

Proprietary Name: EPERZAN; TANZEUM

2. **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

3. **REVIEW DATE: STN 58 March 31, 2014**
59 April 8 2014
60 April 9, 2014

4. **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

5. **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) This issue was first discovered in Dec 2013 not with albiglutide, (b) (4) The investigation was subsequently extended to albiglutide once it was realized that (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)

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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 [redacted] (b) (4) upon completion of the Registration Stability a [redacted] ms. The agency accepts your proposal. However, the agency recommends you to use the [redacted] (b) (4) method to assess the [redacted] (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.

[redacted] (b) (4)

Response from Sponsor:

[redacted] (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**
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

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-1Neutralizing 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:

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
Clinical Pharmacology: Suryanarayana Sista
Statistics: Bo Li
OBP Labeling: NA
RPM: Ray Chiang

4. **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

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:** (b) (4)
12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	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) (4)

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 ❑ 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: ❑ 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 N 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: ❑ 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 usable (e.g. conforms to published guidance)	Y Y Y Y Y Y Y Y	
Companion application received if a shared or divided manufacturing	Y N	N/A

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	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y N	Defer to OBP
❑ Novel Excipients	Y N	Defer to OBP
❑ Executed Batch Records	Y N	Defer to OBP
❑ Method Validation Package	N	Provided in 3.2.S and 3.2.P.
❑ 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]		
❑ general info	Y	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control	Y	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		
❑ control of materials	Y N	Defer to OBP
o raw materials and reagents		
o biological source and starting materials		
o cell substrate: source, history, and generation		
o cell banking system, characterization, and testing		
❑ control of critical steps and	Y	(b) (4)

CTD Module 3 Contents	Present ?	If not, justification, action & status
intermediates o justification of specifications o stability		
❑ 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	Y N	Defer to OBP
❑ control of drug substance o specifications o justification of specs. o analytical procedures o analytical method validation o batch analyses	Y	
❑ reference standards	Y N	Defer to OBP
❑ container closure system	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	Y N	N/A
o container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ 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	Y	

CTD Module 3 Contents	Present ?	If not, justification, action & status
intermediates ❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times) ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin) ❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities) ❑ reference standards or materials ❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s) ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y Y Y Y Y Y Y Y Y Y Y Y	Defer to OBP
Diluent (vials or filled syringes) [3.2P′] ❑ description and composition of diluent ❑ pharmaceutical development o preservative	Y Y Y N	Not applicable.

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	Not applicable.
❑ 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		
❑ 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	Not applicable.
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	Not applicable.
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y		
❑ reference standards	Y	N	Not applicable.
❑ container closure system	Y		
o specifications (vial, elastomer, drawings)			
o availability of DMF & LOAs			
❑ stability	Y		
❑ summary			

CTD Module 3 Contents	Present ?	If not, justification, action & status
❑ post-approval protocol and commitment ❑ pre-approval o protocol o 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 Y N	 Not applicable.
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y Y N Y N	 Defer to OBP Defer to OBP
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N 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	

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: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	 Y Y N Y	 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	

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.

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

/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	Y N	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y N Y N	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
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 N 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 usable (e.g. conforms to published guidance)	Y N Y N Y N Y N Y N Y N Y N	
Companion application received if a shared or divided manufacturing arrangement	Y N	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]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Quality overall summary [2.3]	Y N	
❑ Drug Substance	Y N	
❑ Drug Product	Y N	
❑ Facilities and Equipment	Y N	
❑ Adventitious Agents Safety Evaluation	Y N	
❑ Novel Excipients	Y N	
❑ Executed Batch Records	Y N	
❑ Method Validation Package	Y N	
❑ Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ 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	Y N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y N	
❑ control of critical steps and intermediates o justification of specifications o stability	Y N	
❑ process validation (prospective		

CTD Module 3 Contents	Present?	If not, justification, action & status
plan, results, analysis, and conclusions)	Y N	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
❑ characterization of drug substance	Y N	
❑ control of drug substance o specifications o justification of specs. o analytical procedures o analytical method validation o batch analyses	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y N Y N Y N	
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y N	
❑ pharmaceutical development o preservative effectiveness o container-closure integrity	Y N Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ 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 N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y N	
❑ reference standards or materials	Y N	
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y N	
Diluent (vials or filled syringes) [3.2P′]		
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
o preservative effectiveness	Y N	
o container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation,	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer sterilization validation o 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	
❑ reference standards	Y N	
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF & LOAs	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N	
Other components to be marketed (full description and supporting data, as listed above):		
❑ other devices	Y N	
❑ other marketed chemicals (e.g. part of kit)	Y N	Not Applicable

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

CTD Module 3 Contents	Present?	If not, justification, action & status
Appendices for Biotech Products [3.2.A]		
❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination	Y N	Reviewed by BMAB
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production	Y N	(b) (4) used; most viral testing not applicable.
❑ novel excipients	Y N	
USA Regional Information [3.2.R]		
❑ executed batch records	Y N	
❑ method validation package	Y N	Method validation included in 3.2.S and 3.2.P
❑ comparability protocols	Y N	
Literature references and copies [3.3]	Y N	

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 N	
Includes data demonstrating consistency of manufacture	Y N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	
Data demonstrating comparability of product to be marketed to that used in	Y 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	Y 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.	Y 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: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y N Y N Y N Y 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	Y N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y 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/Team Leader/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