

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201849Orig1s000**

**CHEMISTRY REVIEW(S)**

# **NDA 201849**

## **Glucagon for Injection**

**APP Pharmaceuticals LLC  
(A Division of Fersenius Kabi USA, LLC)**

**MUTHUKUMAR RAMASWAMY, Ph.D.  
OFFICE OF NEW DRUG QUALITY ASSESSMENT**

**(CMC REVIEW FOR THE DIVISION OF ENDOCRINOLOGY AND  
METABOLISM PRODUCTS)**

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## Chemistry Review Data Sheet

**Chemistry Review Data Sheet**

1. NDA            201-849
2. REVIEW #: 1
3. REVIEW DATE: 1-21-14
4. REVIEWER: Muthukumar Ramaswamy, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Chemistry Review #1 for original submission	Aug. 16, 2012
Original Submission	Sep. 30, 2010
Resubmission	Nov. 30, 2011
Amendment 0010	May 31, 2012
Amendment 0012	Jun 27, 2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	Aug. 8, 2014

7. NAME & ADDRESS OF APPLICANT:

Name:	APP Pharmaceuticals (Fresenius Kabi USA= LLC.
Address:	Three Corporate Drive, Lake Zurich, IL 60047
Representative:	Jeremy Rybicki
Telephone:	947-550-2227

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Glucagon for Injection
- b) Non-Proprietary Name (USAN): Glucagon
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)2

10. PHARMACOL. CATEGORY: Hormone; Indicated as diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.

11. DOSAGE FORM: Powder for injection

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 1mg/vial, (reconstituted to 1mg/mL with diluent).
13. ROUTE OF ADMINISTRATION: Intravenous or Intramuscular (b) (4) injection
14. Rx/OTC DISPENSED:  Rx     OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
        SPOTS product – Form Completed  
        Not a SPOTS product

16. CHEMICAL NAME: Glucagon  
 STRUCTURAL FORMULA: His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr.

MOLECULAR FORMULA, C<sub>153</sub>H<sub>225</sub>N<sub>43</sub>O<sub>49</sub>S

MOLECULAR WEIGHT: 3483 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
<span style="background-color: gray; color: gray;">(b) (4)</span>	II	<span style="background-color: gray; color: gray;">(b) (4)</span>	<span style="background-color: gray; color: gray;">(b) (4)</span>	1,4	Adequate	Dec. 9, 2014	LOA Sep.30, 2010; DMF Update dated June 2014
<span style="background-color: gray; color: gray;">(b) (4)</span>	III	<span style="background-color: gray; color: gray;">(b) (4)</span>	<span style="background-color: gray; color: gray;">(b) (4)</span>	3,4	Adequate	Dec. 13, 2011	LOA Sep.30, 2010
<span style="background-color: gray; color: gray;">(b) (4)</span>	III	<span style="background-color: gray; color: gray;">(b) (4)</span>	<span style="background-color: gray; color: gray;">(b) (4)</span>	3,4	Adequate	July 26, 2012	LOA Aug..25, 2009
<span style="background-color: gray; color: gray;">(b) (4)</span>	III	<span style="background-color: gray; color: gray;">(b) (4)</span>	<span style="background-color: gray; color: gray;">(b) (4)</span>	3, 4	Adequate	Feb 28, 2014	LOA Oct. 14, 2010
<span style="background-color: gray; color: gray;">(b) (4)</span>	III	<span style="background-color: gray; color: gray;">(b) (4)</span>	<span style="background-color: gray; color: gray;">(b) (4)</span>	3, 4	Adequate	Apr. 25, 2013	LOA Aug..12, 2010

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

°4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

## Chemistry Review Data Sheet

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	Aug. 25, 2014	NA
Pharm/Tox.	Acceptable	Dec. 9., 2014	Indra Antonipillai
Microbiology	Acceptable	Aug. 15, 2012	John Metcalfe
Labeling	Acceptable	Nov. 03, 2014	DMEPA, OSE

Chemistry Assessment Section

## The Chemistry Review for NDA 201-849

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

From quality perspective, the NDA is recommended for approval.

This approval recommendation is based on the current and past CMC reviews (dated Aug. 16, 2012) for this NDA application, a recommendation for approval from microbiology reviewer Dr. Metcalfe dated Aug. 5, 2012 as well acceptable recommendation from Office of Compliance for the manufacturing facilities associated with this NDA.

Based on CMC review, a 24-month shelf life is granted for the drug product.

##### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

#### II. Summary of Chemistry Assessments

##### A. Description of the Drug Product(s) and Drug Substance(s)

Glucagon, an active ingredient used for manufacturing Glucagon for injection is a synthetic 29 amino acid polypeptide (b)(4). The Applicant has referenced Type II DMF (b)(4) for CMC information related to the drug substance. DMF (b)(4) is adequate to support the manufacturing of the drug product. The Applicant has updated specification for accepting the drug substance, which meets the current USP Glucagon monograph requirements. The proposed specification includes a test for bioidentity, assay of API by HPLC, limits for impurities ((b)(4)), any other Individual Impurity, and Total Impurities)

The proposed drug product is a sterile, lyophilized powder of glucagon filled in 3 mL Type I glass vial and sealed with gray (b)(4) rubber stopper. Each single dose vial contains 1 unit of glucagon, 107 mg of lactose monohydrate NF, (b)(4) Hydrochloric acid and sodium hydroxide are used for pH adjustment to a target pH of (b)(4) prior to lyophilization. (b)(4) For additional details on the proposed drug product manufacturing process description, process controls, batch analysis, reference standard, and stability information, please see Chemistry Review #1 (Dated Aug. 16, 2012 in DARRTS).

The Applicant has updated the drug product specification and included bioidentity specification for drug product (NLT (b)(4) U/mg of Glucagon). The proposed product specification meets current USP monograph for glucagon Injection requirements. The proposed product specification is adequate to control the identity, strength, purity, sterility, and potency of the product. The drug product specification contains limits for two classes of impurities (glucagon related degradants and lactose related degradants). The total Glucagon related impurities (excluding lactose related impurities) are controlled with a limit of NMT (b)(4)%. The total Lactose related impurities, are controlled with a limit of NMT (b)(4)%. Per previous

## Chemistry Assessment Section

CMC review #1 the proposed specifications for impurities are based on process capability, stability data, and toxicology input.

Executive Summary					
From Initial Risk Assessment			Review Assessment		
Product Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Final Risk Ranking	Risk Evaluation	Comment
pH	Formulation Container closure Raw materials Process parameters Scale/equipment Site	Low	Low	Acceptable	In-process controls, (b) (4) Supported by release and stability data.
Appearance	Formulation Container closure Process parameters Scale/equipment Site	Low	Low	Acceptable	Supported by release and stability data from pilot scale batches (1/10 <sup>th</sup> scale).
Reconstitution time	Formulation Container closure Process parameters Scale/equipment Site	Low	Low	Acceptable	Supported by release and stability data from pilot scale batches (1/10th scale). No trends indicated by the stability data.
Water content	Formulation Container closure Process parameters Scale/equipment Site	Low	Low	Acceptable	Supported by release and stability data from pilot scale batches (1/10th scale). No trends indicated by the stability data.
Bioassay	Formulation Analytical methods Container closure Raw materials Process parameters Scale/equipment Site	Medium	Low	Acceptable	Stability data shows bioassay values are within acceptable range (80-120%).

## Chemistry Assessment Section

<p style="text-align: center;">Related Compounds - % Individual and Total impurities</p>	<p style="text-align: center;">Formulation Analytical methods Container closure Raw materials Process parameters Scale/equipment Site</p>	<p style="text-align: center;">Low</p>	<p style="text-align: center;">Low</p>	<p style="text-align: center;">Acceptable</p>	<ol style="list-style-type: none"> <li>1) Levels of impurities are monitored using a validated assay.</li> <li>2) The product stored as powder (to minimize degradation during storage). The reconstituted product will be used immediately before use.</li> <li>3) Stability results for glucagon and related compounds indicate degradation profile comparable to or lower than the reference product</li> </ol>
<p style="text-align: center;">Sterility</p>	<p style="text-align: center;">Formulation Container closure Process parameters Scale/equipment Site</p>	<p style="text-align: center;">Medium</p>	<p style="text-align: center;">Low</p>	<p style="text-align: center;">Acceptable</p>	<ol style="list-style-type: none"> <li>a) Container closure system integrity is verified during release and stability.</li> <li>b) <span style="background-color: gray; color: gray;">(b) (4)</span></li> <li>c) <span style="background-color: gray; color: gray;">(b) (4)</span></li> <li>d) Sterility test per USP &lt;71&gt;</li> </ol>
<p style="text-align: center;">Endotoxin <span style="background-color: gray; color: gray;">(b) (4)</span> content</p>	<p style="text-align: center;">Formulation Container closure Process parameters Scale/equipment Site</p>	<p style="text-align: center;">Medium</p>	<p style="text-align: center;">Low</p>	<p style="text-align: center;">Acceptable</p>	<p style="text-align: center;">USP test Process controls for container closure system</p>
<p style="text-align: center;">Uniformity of dose</p>	<p style="text-align: center;">Formulation Container closure Process parameters Scale/equipment Site</p>	<p style="text-align: center;">Low</p>	<p style="text-align: center;">Low</p>	<p style="text-align: center;">Acceptable</p>	<ol style="list-style-type: none"> <li>a) <span style="background-color: gray; color: gray;">(b) (4)</span></li> <li>b) Uniformity is assured by content uniformity assay (USP &lt;905&gt;).</li> </ol>

Chemistry Assessment Section

Particulate matter	Formulation Container closure Raw materials Process parameters Scale/equipment Site	Low	Medium	Acceptable	a) Test performed per USP <788> b) Stability data for pilot scale batches is supportive of the adequacy of the proposed process controls
Leachables/ /Extractables	Formulation Container closure Process parameters Scale/equipment Site	Low	Low	Acceptable	a) Lyophilized powder. b) Container closure system components used in are in previous applications. Safety of Container closure system were evaluated through USP <381> and <660> tests
Fill Volume	Container closure	Low	Low	Acceptable	Filling process is precise.

Based on original CMC review for this application, a shelf life of 24 months is granted. No stability update has been submitted in the NDA resubmission.

**B. Description of How the Drug Product is intended to be used**

Glucagon for injection is a lyophilized powder, provided in a single dose vial for reconstitution with sterile water for injection immediately prior to use and should not be stored for later use. Each single dose vial contains 1U of glucagon and after reconstitution contains 1U of glucagon /mL. The reconstituted product is intended for intravenous or intramuscular injection. If the solution shows any sign of gel formation or particles, it should be discarded. Each vial contains (b) (4)% overage (to compensate for (b) (4)% unwithdrawable contents in the vials).

The drug product is provided as a 10-vial (b) (4) Store the product at 20° to 25°C (68° to 77°F) protected away from light.

**C. Basis for Approvability or Not-Approval Recommendation**

The CMC section contains adequate information to support the NDA. There are no CMC related deficiencies for this application. The Applicant has voluntarily tightened the specification for impurities and included bioidentity test for drug substance and drug product specification. From CMC review perspective, the NDA is recommended for approval. On 8/15/12, Microbiology reviewer, Dr. Metcalfe has recommended approval of this NDA from microbiology review perspective.

The drug product will be manufactured at Fersenius Kabi USA facility located at 2020 Ruby Street, Melrose Park, Illinois. The Finished product will be tested for release and stability at either above Melrose Park, IL facility or at (b) (4)  
On Aug. 25, 2014, the Office of Compliance has issued an acceptable recommendation for all manufacturing and testing facilities associated with this NDA.

**III. Administrative**

## Chemistry Assessment Section

**A. Reviewer's Signature Recorded electronically****B. Endorsement Block**

DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=PIV,  
serialNumber=D72A10D821086D998790ADA168590108724  
835A1872A8243E8  
Date: 2015.01.21 14:11:45 -05'00'

Chemist Name: Muthukumar Ramaswamy, Ph.D.

Chemistry Team Leader Name: Danae Christodoulou, Ph.D.

Project Manager Name: Meghna Jairath

**C. CC Block Recorded electronically**

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

**NDA 201-849**

**Glucagon for Injection**

**AAP Pharmaceuticals, LLC**

**Olen M. Stephens**

**Division of Metabolism and Endocrinology Products**

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# Chemistry Review Data Sheet

1. NDA 201849
2. REVIEW #: 1
3. REVIEW DATE: 16-Aug-2012
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Application

30-Sep-2010

Resubmission

30-Nov-2011

Amendment 0010

31-May-2012

Amendment 0012

27-Jun-2012

7. NAME & ADDRESS OF APPLICANT:

Name: APP Pharmaceuticals, LLC  
Address: 1501 East Woodfield Road, Suite 300 E  
Schaumburg, IL 60173  
Representative: Heidi Guzalo  
Sr. Manager, Regulatory Affairs  
Telephone: 847-517-5772

## Chemistry Review Data Sheet

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

- a) Proprietary Name: The applicant has not submitted a proprietary name for review. The clinical division considers the lack of a proprietary name as a deficiency due to potential confusion between this Glucagon product that is used for diagnostic purposes and other Glucagon kits that are used in emergency situations.
- b) Non-Proprietary Name (USAN): Glucagon for Injection
- c) Submission Priority: S

**9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) (GlucaGen<sup>®</sup> from Novo Nordisk; NDA 20-918)**

**10. PHARMACOL. CATEGORY:** Indicated as diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract

**11. DOSAGE FORM:** Sterile Powder for Injection

**12. STRENGTH/POTENCY:** 1 mg/vial (IU)

**13. ROUTE OF ADMINISTRATION:** Intravenous, Intramuscular

**14. Rx/OTC DISPENSED:**  Rx  OTC

**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

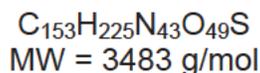
SPOTS product – Form Completed

Not a SPOTS product

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)			Amendment 1/2011, tightening individual impurities to ≤ 1.0%	LOA 30 Sep 2010
	III					8-Mar-2010	LOA 14 Oct 2009
	III					28-Apr-2011	LOA 12 Aug 2010
	III					19-Mar-2010	LOA 25 Aug 2009

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Withhold	22-Feb-2012	Derrick Smith
Pharm/Tox	Acceptable	26-Jul-2012	Indra Antonipillai
Microbiology	Acceptable	15-Aug-2012	John Metcalfe

# The Chemistry Review for NDA 201-849

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

There are no pending CMC review deficiencies to resolve. The overall recommendation from the Office of Compliance for GMP inspections is 'withhold' (22-Feb-2012). Therefore, the CMC recommendation for NDA 201-849 is for complete response pursuant the OC recommendation.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has agreed to tighten release and stability specifications for individual impurities, total glucagon related impurities, total lactose related impurities, assay by HPLC, and mass balance to reflect manufacturing capability as manufacturing experience is gained. Re-evaluation of specifications should occur after the 10<sup>th</sup> commercial batch. This is not a PMC or PMR.

Note that the application is receiving a complete response due to clinical pharmacology deficiencies. Because the applicant will need to conduct additional studies to address the clinical pharmacology deficiencies, it may be possible to address the drug product specifications when the application is re-submitted because additional batch data may be available at that time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Glucagon is the active ingredient for Glucagon for Injection (NDA 201-849) (b) (4). The drug substance for GlucaGen® is manufactured by (b) (4) but the drug substance for NDA 201-849 is (b) (4). The inactive ingredients (lactose NF and Water for Injection USP) are the same as those used in GlucaGen®. (b) (4) and (b) (4) are also used as processing aids for the drug product, but will not appear in the label. All the excipients are compendial quality. An overage of (b) (4) % was used for the registration batches for Glucagon for Injection, which includes (b) (4) % unwithdrawable contents. The lyophilized drug product is stored in a 3 mL Type I glass vial with a 13 mm gray (b) (4) rubber stoppers. (b) (4)

(b) (4) Under these conditions, two classes of impurities are generated, glucagon related degradants and lactose based degradants. (b) (4)

## Executive Summary Section

(b) (4)

Qualification of the (b) (4) was a review issue for the toxicology reviewer, who recommended that the drug substance specification be reduced from NMT (b) (4)% as proposed by the applicant to NMT (b) (4)%. The lactose related degradants (b) (4)

Of these impurities, (b) (4) were observed in both the APP Pharmaceutical product and reference product. (b) (4) were observed in the heat stressed samples, but not those stored under long term conditions. No identity was determined for (b) (4) because of low signal strength.

The drug product is stored at room temperature and is supported by 24 months of stability data at 25°C/60% RH and 6 months of stability data at 40°C/75% RH for a 2 year shelf life.

**B. Description of How the Drug Product is Intended to be Used**

Glucagon for Injection is provided as a lyophilized powder that is reconstituted prior to administration with sterile water for injection to yields 1 mg/mL (1 unit/mL) solution. Each vial of lyophilized powder contains a (b) (4)% overage of glucagon to account for unwithdrawable contents. The drug product can be provided as a (b) (4) or as a 10 vial (b) (4). The dose administered ranges from 0.2 mg to 2 mg depending on the diagnostic technique and route of administration (intramuscular or intravenous). The drug product is administered by prescription only. A 24 month shelf life is granted when stored at 20°C to 25°C (68°F to 77°F). The product should not be frozen and should be protected from light prior to administration.

**C. Basis for Approvability or Not-Approval Recommendation**

Chemistry, Manufacturing and Controls deficiencies for the drug substance and drug product have been adequately addressed. There are no CMC review deficiencies, but the OC has rendered a "withhold" recommendation (22-Feb-2012). Therefore, the CMC recommendation is for a complete response.

**III. Administrative**

- A. Reviewer's Signature**
- B. Endorsement Block**
- C. CC Block**

Olen Stephens  
Su Tran/Ali Al-Hakim  
Khushboo Sharma

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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OLEN M STEPHENS

08/16/2012

CMC Recommendation is for a complete response due to withhold recommendation from OC

ALI H AL HAKIM

08/16/2012

Initial Quality/CMC Assessment  
ONDQA

**Division of Metabolism and Endocrinology Products**

**NDA:** 201849

**Applicant:** APP Pharmaceuticals LLC

**Stamp Date:** 05-DEC-2010

**PDUFA Date:** 05-AUG-2011

**Proposed Proprietary Name:** [none]

**Established Name:** Glucagon

**Dosage form and strength:** Powder for injection (to be reconstituted with (b) (4)

Sterile Water for Injection)

1 mg

**Route of Administration:** IM, (b) (4) or IV injection

**Indications:** (b) (4)

diagnostic aid during radiologic examinations to temporarily inhibit movement of the GI tract

**CMC Lead:** Su (Suong) Tran, ONDQA

**ONDQA Fileability:** Yes

Initial Quality/CMC Assessment  
ONDQA

CONSULTS/ CMC RELATED REVIEWS	COMMENT
CBER	<i>Not applicable</i>
CDRH	<i>Not applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
Compliance (DMPQ)	EER was sent to Compliance by ONDQA PM on 29-OCT-2010.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	Review of sterility assurance.
OBP	<i>Not applicable</i>
ONDQA Biopharm	<i>Not applicable (per A. Dorantes)</i>
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Pharm/Tox	Review of qualification information on specific impurities.
QbD	<i>Not applicable</i>

This is an electronic NDA, filed as a 505(b)(2) application, with Glucagen as the reference listed drug (listed in Form 356h). The reference drug is recombinant, while the new drug is synthetic. There is no associated IND.

**Table 6. Formulation Data: Side-by-Side Comparison of the Reference Listed and Proposed Drug**

	Reference Listed Drug	Proposed Drug Product
Name	GlucaGen <sup>®</sup>	Glucagon for Injection
Active Ingredient	Glucagon	Glucagon
Strength	1 mg/vial (1 IU)	1 mg/vial (1 IU)
<b>Excipient (amount/1-mg vial)<sup>1</sup></b>		
Lactose Monohydrate	107 mg	107 mg
Hydrochloric Acid	As required for pH adjustment	As required for pH adjustment
Sodium Hydroxide	As required for pH adjustment	As required for pH adjustment

(b) (4)

<sup>1</sup> APP's excipients are all compendial grade materials.

(b) (4)

Reference is made to the DMF (b) (4) for the CMC information on the drug substance.

The drug product is a lyophilized sterile powder to be reconstituted with (b) (4) Sterile Water for Injection for immediate administration. (b) (4)

The product will be packaged in single-use vials of 1 mg. The product is stored at room temperature.

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Has all information requested during the IND phases, and at the pre-NDA meetings been included?  
No IND was submitted to FDA.

**Drug substance:**

<b>Nomenclature:</b>	Glucagon
<b>Molecular Structure:</b>	Glucagon is a single-chain polypeptide containing 29 amino acid residues: His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr
<b>Molecular Formula:</b>	C <sub>153</sub> H <sub>225</sub> N <sub>43</sub> O <sub>49</sub> S
<b>Molecular Weight:</b>	3483

**Table 1. Physicochemical Properties of the Drug Substance**

Properties	Description of Properties
Appearance	White powder
Specific Rotation	(b) (4)
Solubility Profile	(b) (4)
Polymorphs	(b) (4)

Reference is made to the DMF (b) (4) for all CMC information on the drug substance.

**Review comments:**

- The drug substance specification (copied on pages 9-11 of this review) is based on the current USP monograph for biologically-derived glucagon, with the addition of Appearance, Identification by SDS-PAGE, Specific Rotation, Amino acid Analysis, Chloride/ Acetate/ Ammonium Content, Peptide Content, Mass Balance, Residual Solvents, Bioburden, and Bacterial Endotoxins. As previously indicated by FDA for a different glucagon NDA, identification testing by amino acid analysis is adequate for a small and simple peptide such as glucagon (i.e., it is not necessary to include a more complex test such as peptide mapping in the drug substance specification).
- The peptide content is calculated from the nitrogen test. Per FDA's guidance on the risk for (b) (4) contamination, the applicant validated a limit test for the (b) (4) content (FDA's

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limit = (b) (4) ppm) but does not include this attribute in the drug substance specification. The reviewer will evaluate the data to determine whether this test should be included in the specification. Alternatively, the applicant could use a test other than the nitrogen test to calculate the peptide content.

- The proposed limits on impurities are copied below, with the structure of the one identified impurity (b) (4). The limits are above CDER's identification and qualification thresholds of 0.50% and 1.00% for peptide impurities. The applicant states that the USP monograph has a limit of (b) (4)% for a single impurity. However, this justification is not acceptable for a new product submitted in a 505(b) application. In the drug product technical section of the NDA, the applicant includes a "Toxicity review and risk assessment" report for the glucagon-related degradants/impurities in section 3.2.P.5.6. The reviewer will consult with the PharmTox team in determining appropriate limits on both the peptide-related impurities.

Related Peptides	
A. (b) (4)	A. NMT (b) (4)%
B. Any Other Individual Impurity	B. NMT %
C. Total Impurities	C. NMT %

Impurity Name	Structure	Origin
(b) (4)		

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**Drug product**

RLD		APP		Function of Ingredients
Ingredients	Amount	Ingredients	Amount	
Glucagon	1 unit	Glucagon	1 unit	Active Pharmaceutical Ingredient
Lactose Monohydrate	107 mg	Lactose Monohydrate, NF	107 mg	(b) (4)
Hydrochloric Acid	As required	Hydrochloric Acid, NF	As required	pH adjuster
Sodium Hydroxide	As required	Sodium Hydroxide, NF	As required	pH adjuster

**Table 1. Component Composition per Unit Dose, Exhibit Batch and Maximum Commercial Batch Sizes: Product Code 509603**

Glucagon for Injection	Unit Dose	Exhibit Batches			Proposed Commercial Batch
		R107-002	C108-002 <sup>5</sup>	C109-002 <sup>5</sup>	
Strength	1 mg				
Packaging Configuration	1 mg in a 3-mL vial				
Product Code	509603				
Batch Size (L)	N/A	(b) (4)		(b) (4)	
Batch Size (vials)	N/A	(b) (4)		(b) (4)	
Ingredient	Ingredient Amount/vial	Ingredient Amount/Batch		Ingredient Amount/Batch	
Glucagon	1 unit <sup>1</sup>	(b) (4)			
Lactose Monohydrate, NF	107 mg	(b) (4)			
Hydrochloric Acid, NF	as required	(b) (4)			
Sodium Hydroxide, NF	as required	(b) (4)			

<sup>1</sup> 1 Unit Glucagon is equivalent to 1 mg Glucagon.

<sup>5</sup> Please note that C108-002 and C109-002 have a suffix of "S" in the stability summaries data; this is to distinguish the batches being differentiated between stability and clinical testing.

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**Review comments:** (The drug product specification is copied on pages 12-14 of this review)

- [REDACTED] (b) (4)  
[REDACTED]
- **Formulation development.** [REDACTED] (b) (4)  
[REDACTED]
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** Three drug product batches with the commercial formulation were manufactured at 1/5 the commercial scale at the commercial manufacturing site, packaged in the commercial primary container closure system. All three batches (R107-002, C108-002, C109-002) are primary stability batches, and the C109-002 batch was used in the pivotal BE study 20090101.
- **Comparative characterization of the new drug and the referenced drug.** Similarity assessment of the 2 products was performed by amino acid sequencing (by Edman degradation), average molecular weights (by HPLC-MS), potency assay (USP method), and impurity testing (single and total). The applicant states that [REDACTED] (b) (4)  
[REDACTED]  
See the 74-day letter comment at the end of this review. The reviewer will evaluate all available information to determine whether [REDACTED] (b) (4)
- **Assay.** The USP bioassay method in the “Glucagon for Injection” monograph is used.
- **Limits on degradation products.** The proposed limits are copied on the next page, with the structures of the one identified degradant Lactose-Related Impurity [REDACTED] (b) (4) and of another identified lactose-related degradant, [REDACTED] (b) (4), that is not included in the proposed specification. Both the peptide-related impurity limit and lactose-related impurity limit are above CDER’s and ICH’s identification and qualification thresholds of 0.50% and 1.00%. The applicant includes a “Toxicity review and risk assessment” report for the glucagon-related degradants/impurities in section 3.2.P.5.6. According to this report, [REDACTED] (b) (4) [REDACTED] contains structural elements that are potentially hepatotoxic and mutagenic. Currently the proposed specification does not include any limit on this compound.  
See the 74-day letter comment at the end of this review. The reviewer will consult with the PharmTox team in determining appropriate limits on both the peptide-related and lactose-related degradants.

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Impurities:	
A. Glucagon-Related Impurities	A. NMT (b) (4)
B. Total Impurities (excluding lactose-related impurities)	B. NMT %
C. Lactose-Related Impurity (b) (4)	C. NMT
D. Other Lactose-Related Impurity	D. NMT

(b) (4)

(b) (4)

- Manufacture.** The manufacturing process is (b) (4)
- Master batch records** are included in the NDA for the commercial manufacturing process (complying with 505(b)(2) regulations).
- Container closure system.** Reference is made to several DMFs for the packaging components. The reviewer will review the information in the NDA and DMFs in determining whether there is sufficient safety information on the product-contact components per FDA's guidance on container closure systems for an injectable powder.

Vial:	3-mL Type I, (b) (4) glass vial with a 13-mm finish
Stopper:	13-mm, (b) (4) rubber (b) (4) stopper
Seal:	13-mm, aluminum crimp with a plastic flip-cap
Secondary Packaging:	(b) (4)

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- **Stability.** As mentioned earlier in this review, three drug product batches with the commercial formulation were manufactured at 1/5 the commercial scale at the commercial manufacturing site, packaged in the commercial primary container closure system. All three batches (R107-002, C108-002, C109-002) are primary stability batches. The product will be stored at room temperature.

Six-months accelerated ( $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$ ), along with twenty-four months (R107-002), eighteen months (C108-002, C109-002) controlled room temperature ( $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$ ) stability studies of the drug product have been completed per the conditions and schedule presented in **SECTION 3.2.P.8.1.1**. The **STABILITY DATA** from these studies are well within the specification and are provided in this NDA 505(b)(2) application.

No in-use stability study was conducted for the reconstituted product. Therefore, the labeling will state that the reconstituted product is for immediate-use only. A photostability study was conducted and the applicant states in the pharmaceutical development report [REDACTED] <sup>(b) (4)</sup>. However, no result is included in the NDA in support of this statement. In addition, in the manufacturing process section of the NDA, the applicant states “This drug product is light sensitive and should be protected from exposure to light [REDACTED] <sup>(b) (4)</sup> See the 74-day letter comment at the end of this review.”

- **Comparability protocol.** None.

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**Table 4. Regulatory Specification for Glucagon**

Test	Acceptance Criteria	Test Method <sup>1</sup>	Lot #0604296 Mfr Lot #1003060	Lot #0809590 Mfr Lot #1014789
Appearance	White powder	Visual Examination	White powder	White powder
Appearance of Solution A. 8 mg/mL solution in 0.1 N HCl B. 10 mg/mL solution in 0.01 N HCl	A. Clear and Colorless B. Clear and Colorless	Visual Examination: Vortex and sonicate to help dissolving and eliminating foam. Compare to the corresponding diluents in similar glassware.	A. Meets requirements B. Meets requirements	A. Meets requirements B. Meets requirements
Identification: A. SDS-PAGE B. HPLC	A. The principal band in the electropherogram of the test solution has a relative mobility ( $M_B$ ) that is within (b)(4)% of that of the Glucagon CRS. B. The retention time of the major peak in the chromatogram of the Raw Material Sample Preparation corresponds to that of the major peak in the chromatogram of the Standard Preparation and the Ratio (R) of the retention times is: (b)(4)	A. 10-08-01-6251 B. 10-08-01-6252 10-08-03-6113	A. $M_B$ (Assay) 0.84 $M_B$ (Std) 0.86 Meets requirements B. $T_R$ (Sample) 32.226 min $T_R$ (Std) 32.226 min R = 1.00 Meets requirements	A. $M_B$ (Assay) 0.85 $M_B$ (Std) 0.84 Meets requirements B. $T_R$ (Sample) 35.863 min $T_R$ (Std) 35.812 min R = 1.00 Meets requirements
Specific Rotation	(b)(4)	USP <781S> 10-08-05-6021	-29.5°	-32.8°
Water Content	NMT (b)(4)%	USP <921> Method Ia 10-08-05-6004	(b)(4)	
Residue on Ignition	NMT (b)(4)%	USP <281> 10-08-05-6013		

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Amino Acid Analysis (Molar Ratio Ala=1.00)	Arg	(b) (4)	CON-IM-0059 Tested by (b) (4)	(b) (4)	
	Glx				
	His				
	Lys				
	Phe				
	Thr				
	Tyr				
	Asx				
	Gly				
	Leu				
	Met				
	Ser				
	Trp				
Val					
(b) (4)	NMT (b) (4)		10-08-01-6258		
(b) (4)	NMT (b) (4) ppm		10-08-01-6259	NMT (b) (4) ppm	NMT (b) (4) ppm
(b) (4)	NMT (b) (4) %		10-08-01-6254	(b) (4)	
(b) (4)	NMT (b) (4) %		09D05-7 Tested by (b) (4)		
(b) (4)	(b) (4) %		USP <461> Method II 10-08-01-6257		
(b) (4)	NLT (b) (4) %		10-08-01-6257		
Mass Balance	(b) (4) %		10-08-01-6257		
Related Peptides:			10-08-01-6252		
A. (b) (4)	A. NMT (b) (4) %				
B. Each Individual Impurity	B. NMT (b) (4) %				

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C. Total Impurities	C. NMT (b) (4) %		(b) (4)
Assay	0.80 – 1.25 USP Unit/mg (as-is basis)	16E-13 Tested by (b) (4)	(b) (4)
Microbial Bioburden	A. Total Aerobic Count	NMT (b) (4) CFU/g	USP <61> 01-10-05-0004
	B. Total Yeast and Mold Count	NMT (b) (4) CFU/g	USP <61> 01-10-05-0004
Bacterial Endotoxin	NMT (b) (4) EU/mg		USP <85> 01-10-08-0011

<sup>1</sup> References to compendia signify current compendia. If a compendial monograph or test changes, APP will implement the changes and report them via annual report.

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**Table 1. Regulatory Specifications for Glucagon for Injection**

Test	Specification	Test Method <sup>1</sup>
Description	Lyophilized white powder in a (b) (4) glass vial	Visual Examination
Reconstitution Time	NMT (b) (4) minutes Reconstitute with 1.0 mL of WFI or Purified Water, USP	10-08-05-6005
Constituted Solution		
A. Completeness	A. The solid dissolves completely, leaving no visible residue as undissolved matter.	A. USP <1> 10-08-05-6005
B. Clarity	B. Clear	B. USP <1> 10-08-05-6005
C. Particulate Matter	C. The constituted solution is essentially free from particles of foreign matter that can be observed on visual inspection.	C. USP <1> 10-08-05-6005
D. Visual Color	D. Colorless	D. 10-08-05-6005
Instrumental Color (b) (4)	NMT (b) (4)	99-08-00-6016 01-08-07-0020
pH	1.7 – 3.5	USP <791> 10-08-05-6001
Water Content	NMT (b) (4) %	USP <921> <i>Method 1A</i> 10-08-05-6004
Uniformity of Dosage Units <sup>3</sup> (Weight Variation)	Meets the requirements of USP <905>	USP <905> 10-08-03-0001
Container/Closure Integrity <sup>4</sup> ICP Method	The (b) (4) concentration in each test sample is NMT the average of the two positive controls.	<b>10-08-00-6015</b> and <b>10-08-03-6274</b>

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Test	Specification	Test Method <sup>1</sup>
Identification <sup>3</sup> A. SDS-PAGE  B. HPLC	A. The principal band in the electropherogram of the Glucagon for Injection solution has a relative mobility ( $M_R$ ) that is within (b)(4)% of that of the Glucagon In-house Reference Standard.  B. The retention time of the major peak in the chromatogram of the Finished Product Sample corresponds to that of the Standard Preparation and the Ratio (R) of the retention times is (b)(4)	A. 10-08-01-6251  B. 10-08-03-6281 and 10-08-03-6113
Assay Label Claim: 1 mg/vial	(b)(4)	USP (b)(4)
Impurities: A. Glucagon-Related Impurities B. Total Impurities (excluding lactose-related impurities) C. Lactose-Related Impurity (b)(4) D. Other Lactose-Related Impurity	A. NMT (b)(4)% B. NMT (b)(4)% C. NMT (b)(4)% D. NMT (b)(4)%	10-08-03-6281
Particulate Matter	(b)(4) um: NMT (b)(4) particles/container (b)(4) um: NMT (b)(4) particles/container	USP <788> 99-08-03-6058 01-08-05-0788
Bacterial Endotoxins	NMT (b)(4) EU/mg of glucagon	USP <85> 01-10-08-0003

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Test	Specification	Test Method <sup>1</sup>
Sterility	Sterile	USP <71> 01-10-07-0001
Other Requirements Test <sup>3</sup>	Meets the requirements of USP <1>	USP <1>
Statement of Compliance to USP <467> <sup>5</sup>	This finished drug product complies to the USP <467> General Chapter for Residual Solvents per Option 1.	

<sup>1</sup> References to compendia signify current compendia. If a compendial monograph or test changes, APP Pharmaceuticals, LLC (APP) will implement the changes and report them via annual report. Where both the compendial test method and an APP test method are cited, the APP method is the APP-internalized version of the compendial method. Multiple internal methods for a non-product-specific test reflect methods that were developed in product development. (b) (4) site-specific QC method (-

<sup>2</sup> (b) (4) performs the bioassay for APP. Their method 16E-13 is the USP method.

<sup>3</sup> Release test only.

<sup>4</sup> Release test was performed for exhibit lot #R107-002, as the exhibit lot was tested prior to the *February 2008 Guidance for Industry: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol of Sterile Products*. Exhibit lots #C108-002 and #C109-002 have CCIT testing performed annually and expiry in accordance with the above mentioned *February 2008 Guidance for Industry: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol of Sterile Products*.

<sup>5</sup> (b) (4)

**Supporting NDA or IND: none**

**Supporting DMFs:**

3.2 Drug Master Files

Drug Substance: (b) (4)  
Type II, DMF # (b) (4)

Vial: (b) (4)  
Type III, DMF # (b) (4)

(b) (4)  
Type III, DMF # (b) (4)

Stopper: (b) (4)  
Type III, DMF # (b) (4)

**GMP facilities:** EER was sent to Compliance by ONDQA PM on [pending date].

*This copied information is from the 18-OCT-2010 amendment with a revised 356h:*

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**Table 1. Manufacturing and Testing Facilities for the Drug Substance and Drug Product**

Facility Name	Address	Contact Information	CFN/EIN	Responsibilities
(b) (4)				

Facility Name	Address	Contact Information	CFN/EIN	Responsibilities
APP Pharmaceuticals, LLC	2020 Ruby Street Melrose Park, IL 60160	Anne Huffman, Sr. Director of QA/QC Phone: (708) 345-6170 Fax: (708) 450-7563 Email: ahuffman@APPpharma.com	1450022	FP manufacturing, release/stability testing, and packaging; API release testing
APP Pharmaceuticals, LLC	2045 North Cornell Avenue Melrose Park, IL 60160	David Bowman, VP of Product Development Phone: (708) 343-6100 Fax: (708) 486-2095 Email: dbowman@APPpharma.com	1421790	Product development, and alternate API release, and FP release/stability testing
APP Pharmaceuticals, LLC	8045 Lamon Avenue, Suite 300 Skokie, IL 60077	David Bowman, VP of Product Development Phone: (708) 343-6100 Fax: (708) 486-2095 Email: dbowman@APPpharma.com	Not Available	Product development, and alternate API release, and FP release/stability testing
APP Pharmaceuticals, LLC	3159 Staley Road Grand Island, NY 14072	Tom Golich, Senior Director of QA/QC Phone: (787) 621-5000 Fax: (787) 621-5193 Email: tgolich@APPpharma.com	1321116	Alternate API release, and FP release/stability testing

(b) (4)

Facility Name	Address	Contact Information	CFN/EIN	Responsibilities
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(b) (4)

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**PRODUCT QUALITY**  
**FILING REVIEW FOR NDA (ONDQA)**

NDA Number: 201849

Established/Proper Name: Glucagon

Applicant: APP  
Pharmaceuticals LLC

Letter Date: 30-SEP-2010

Stamp Date: 05-OCT-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			No IND was submitted.
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

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8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	x		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>
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	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
<b>D. drug substance/active pharmaceutical ingredient (DS/api)</b>				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to DMF.
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to DMF.
15.	Does the section contain controls for the DS?			Reference is made to DMF.
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to DMF.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	
<b>E. drug product (dp)</b>				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		See Comment at the end of this review.
G. microbiology				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	x		The information is in the Quality module.
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	x		See the next page.

*{See appended electronic signature page}*

Su (Suong) Tran  
CMC Lead  
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

*{See appended electronic signature page}*

Ali Al Hakim  
Branch Chief  
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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**CMC comments for the 74-day letter**

1. Provide the data discussed in section 3.2.P.5.5 (to include tabulated data and chromatograms) that show the comparison of impurities/degradants in your product and GlucaGen, with the impurities/degradants clearly identified.
2. According to the toxicity review and risk assessment report included in the NDA, (b) (4) contains structural elements that are potentially hepatotoxic and mutagenic. Justify the lack of any limit on this compound in the proposed drug product specification.
3. It is stated in the pharmaceutical development report that photostability data show that (b) (4). However, it is stated in the manufacturing process section that “This drug product is light sensitive and should be protected from exposure to light (b) (4). Submit photostability data on the lyophilized product and the reconstituted product.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUONG T TRAN  
11/23/2010

ALI H AL HAKIM  
11/23/2010