

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201849Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201849

SUPPL # 000

HFD #

Trade Name N/A

Generic Name glucagon for injection

Applicant Name Fresenius Kabi USA, LLC

Approval Date, If Known May 8, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The applicant conducted study AA9843, "Bioequivalence of a Test Formulation of Glucagon for SC Injection Compared to Glucagon for Injection (Bedford Laboratories) Under Fasted Conditions."

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the

NDA #(s).

NDA# 020918 GlucaGen (glucagon for injection)

NDA# 020928 glucagon injection

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets

"clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted

or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
! YES
! NO
! Explain: ! Explain:

Investigation #2
!
! YES
! NO
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Elisabeth A. Hanan, M.S.
Title: Regulatory Project Manager
Date: May 8, 2015

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ELISABETH A HANAN
05/08/2015

JEAN-MARC P GUETTIER
05/08/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 201849 BLA #	NDA Supplement # 000 BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: none Established/Proper Name: glucagon Dosage Form: sterile lyophilized powder for injection		Applicant: Fresenius Kabi USA LLC Agent for Applicant (if applicable): N/A
RPM: Elisabeth Hanan		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>May 8, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR 09/27/2012; RTF 12/03/2010
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 5 – New Formulation or New Manufacturer
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP 05/08/2015 CR 09/27/2012; RTF 12/03/2010
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included – see labeling attached to AP letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included - see labeling attached to AP letter
❖ Proprietary Name	N/A
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 09/18/2014 DMEPA: <input type="checkbox"/> None 04/23/2015; 12/23/2014; 11/03/2014; 09/07/2012 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 04/22/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i> ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review not completed for previous cycles <input type="checkbox"/> Not a (b)(2) 04/16/2015
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)	
○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	<input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>)	N/A
• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>This application does not trigger PREA</u>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Teleconference 06/07/2012
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg Post-CR 12/27/2012 Post-RTF 03/24/2011
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Mid-cycle Communication (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 05/08/2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	05/01/2015; 09/24/2012 (CDTL Review); 01/18.2012; 2/22/2011; 11/30/2010
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 12 of Clinical review dated 05/01/2015 Page 9 of CDTL review dated 09/24/2012
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 03/26/2015
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04/01/2015; 08/27/2012; 01/20/2012; 05/03/2011
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested 01/05/2015; 09/04/2012

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/09/2014; 07/26/2012; 02/01/2012; 11/16/2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 01/21/2015; 08/16/2012; 11/23/2010
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 08/15/2012; 01/03/2012; 11/23/2010
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Page 54 of Product Quality review dated 08/16/2012
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: 08/25/2014 (see Product Quality Review dated 01/21/2015, pages 5 and 20) <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done N/A
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

ELISABETH A HANAN
05/08/2015

From: Hanan, Elisabeth
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: RE: NDA 201849 (Glucagon for Injection) Labeling Comments
Date: Wednesday, May 06, 2015 2:31:26 PM

Hi Jeremy,

This is to confirm receipt of your email. We note your agreement to the labeling dated May 6, 2015.

Thank you,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

From: Jeremy.Rybicki@fresenius-kabi.com [mailto:Jeremy.Rybicki@fresenius-kabi.com]
Sent: Wednesday, May 06, 2015 1:59 PM
To: Hanan, Elisabeth
Subject: Re: NDA 201849 (Glucagon for Injection) Labeling Comments

Hi Elisabeth,

I am confirming receipt of the draft labeling with comments from the Agency. We agree with all of the revisions.

Can you please confirm receipt of this email?

Sincerely,
Jeremy

Jeremy Rybicki
Manager, I&D Regulatory Affairs

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847.550.2227
F: +1 847-550-7120
C: (b) (6)
Jeremy.Rybicki@fresenius-kabi.com
www.fresenius-kabi.us

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From: "Hanan, Elisabeth" <Elisabeth.Hanan@fda.hhs.gov>
To: "Jeremy.Rybicki@fresenius-kabi.com" <Jeremy.Rybicki@fresenius-kabi.com>,
Date: 05/06/2015 12:28 PM
Subject: NDA 201849 (Glucagon for Injection) Labeling Comments

Good afternoon,

FDA has compiled the attached comments for your draft labeling submitted via email for the above-mentioned NDA on May 5, 2015.

If you agree with our edits, we request that you respond to this email stating that you agree with all of the revisions. There is no need to submit a revised version of the draft label via email unless you are proposing additional changes. If you are proposing additional revisions, then any proposed changes from the attached version should be marked via tracked changes.

We request a response by noon on **Thursday, May 7, 2015**.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

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/s/

ELISABETH A HANAN
05/06/2015

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (Glucagon for Injection) Labeling Comments
Date: Wednesday, May 06, 2015 1:28:18 PM
Attachments: [NDA 201849 Glucagon Package Insert - FDA Comments 06May2015.doc](#)

Good afternoon,

FDA has compiled the attached comments for your draft labeling submitted via email for the above-mentioned NDA on May 5, 2015.

If you agree with our edits, we request that you respond to this email stating that you agree with all of the revisions. There is no need to submit a revised version of the draft label via email unless you are proposing additional changes. If you are proposing additional revisions, then any proposed changes from the attached version should be marked via tracked changes.

We request a response by noon on **Thursday, May 7, 2015**.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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/s/

ELISABETH A HANAN
05/06/2015

From: [Hanan, Elisabeth](mailto:Elisabeth.Hanan@fda.hhs.gov)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: RE: NDA 201849 (Glucagon for Injection) Labeling Comments
Date: Tuesday, May 05, 2015 4:19:47 PM

Hi Jeremy,

I have conferred with our team and we agree with retaining the 2 mg intramuscular dose information in Table 3 for consistency with the Dosage and Administration section.

In addition, we would like to retain footnote (a) to Table 3, but propose changing the text to the following for consistency with the Dosage and Administration section:

Select from these doses based on type of diagnostic procedure, route of administration and procedure duration.

Due to the additional discussion today, if you would be able to provide your revised label by noon tomorrow, that would be acceptable.

Thank you,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

From: Jeremy.Rybicki@fresenius-kabi.com [mailto:Jeremy.Rybicki@fresenius-kabi.com]
Sent: Tuesday, May 05, 2015 12:12 PM
To: Hanan, Elisabeth
Subject: Re: NDA 201849 (Glucagon for Injection) Labeling Comments

Hi Elisabeth,

We came upon a possible discrepancy. We would like to keep the PD related information on the 2 mg dose in Table 3, since our D&A, section 2.1 has a 2 mg dose listed for IM use.

Is this something you would like for us to annotate in the PI that we object or reject the Agency's redline on that point?

Thank you,
jeremy

Jeremy Rybicki
Manager, I&D Regulatory Affairs

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847.550.2227
F: +1 847-550-7120
C: (b) (6)
Jeremy.Rybicki@fresenius-kabi.com
www.fresenius-kabi.us

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From: "Hanan, Elisabeth" <Elisabeth.Hanan@fda.hhs.gov>
To: "Jeremy.Rybicki@fresenius-kabi.com" <Jeremy.Rybicki@fresenius-kabi.com>,
Date: 05/04/2015 10:32 AM
Subject: NDA 201849 (Glucagon for Injection) Labeling Comments

Good morning,

FDA has compiled the attached comments for your draft labeling submitted via email for the above-mentioned NDA on April 24, 2015. We request that you accept all proposed changes that you agree with and return a revised label by close of business on **Tuesday, May 5, 2015**. Any proposed changes from this version should be marked via tracked changes.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

[attachment "NDA 201849 Glucagon Package Insert - FDA Comments 04May2015.doc" deleted by Jeremy Rybicki/RA/SC/US/HHC/Fresenius]

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/s/

ELISABETH A HANAN
05/05/2015

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (Glucagon for Injection) Labeling Comments
Date: Monday, May 04, 2015 11:31:57 AM
Attachments: [NDA 201849 Glucagon Package Insert - FDA Comments 04May2015.doc](#)

Good morning,

FDA has compiled the attached comments for your draft labeling submitted via email for the above-mentioned NDA on April 24, 2015. We request that you accept all proposed changes that you agree with and return a revised label by close of business on **Tuesday, May 5, 2015**. Any proposed changes from this version should be marked via tracked changes.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

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ELISABETH A HANAN
05/04/2015

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (Glucagon for Injection) Labeling Comments
Date: Thursday, April 23, 2015 4:15:53 PM
Attachments: [NDA 201849 Glucagon Package Insert - FDA Comments 23Apr2015.doc](#)

Good afternoon,

FDA has compiled the attached comments for your draft labeling submitted via email for the above-mentioned NDA on April 13, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised label via email for our final review by close of business on **Monday, April 27, 2015**. Any proposed changes from this version should be marked via tracked changes.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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ELISABETH A HANAN
04/23/2015

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (glucagon) Labeling Comments
Date: Thursday, April 16, 2015 5:45:43 PM

Good evening,

With regards to the draft PI submitted by email on April 13, 2015, we have the following request:

The Figures 1A and 1B need to be re-plotted to depict only the PK/PD profiles of the Fresenius Kabi (FK) glucagon product. The concentration-time profile of the reference product should be deleted. The concentrations from the two replicate treatment periods of the FK glucagon product should be averaged to show one curve for mean baseline-corrected glucose over time (Fig 1A) and mean baseline un-corrected glucagon over time (Fig 1B), respectively.

We request that you provide a revised draft of the PI by noon on Monday, April 20. Submission of this revised draft via email will be acceptable. Please let me know if you have any questions.

Thank you,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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/s/

ELISABETH A HANAN
04/16/2015

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Cc: Molly.Rapp@fresenius-kabi.com
Subject: NDA 201849 (Glucagon for Injection) Labeling Comments
Date: Monday, April 06, 2015 10:44:25 AM
Attachments: [NDA 201849 Glucagon Package Insert - FDA Comments 06Apr2015.doc](#)

Good morning,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on August 8, 2014. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised label no later than **Monday, April 13, 2015**. All of your proposed changes from this version should be marked via tracked changes.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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ELISABETH A HANAN
04/06/2015

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (glucagon) Information Request
Date: Friday, February 13, 2015 12:30:44 PM

Good afternoon,

Regarding your submission dated December 19, 2014, in the source data sets for the individual subject concentrations for plasma glucose, the data is presented in pg/mL. Similarly, in the study report (GLUC-002-CP1) the plasma glucose is presented as pg/mL (Figure 2, Page 34). However, the individual and mean pharmacodynamics parameters are listed as µg/mL or µg*hr/mL. The bioanalytical validation reports also indicate plasma glucose concentrations in µg/mL. The concentration units should be consistent with the bioanalytical validation. Address this discrepancy and send the corrected raw data sets, Tables, and Figures.

Please confirm receipt of this request and send this information by February 18, 2015.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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ELISABETH A HANAN
02/13/2015

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (glucagon) Information Request
Date: Tuesday, January 13, 2015 1:26:57 PM

Good afternoon,

Regarding your NDA resubmitted on August 8, 2014, for glucagon for injection, we have the following information request:

Please complete Tables 1-4 as described below. They relate to the four subjects listed who completed only Period 1 of the study.

Table 1. Uncorrected Plasma Glucose Concentrations (pg/mL) following Drug A or Drug B

	Sample times (hr)						
Subject #	Predose	0.08	0.17	0.25	0.33	0.42	0.5
5							
9							
28							
31							

Table 2. Uncorrected Plasma Glucagon Concentrations (pg/mL) following Drug A or Drug B

	Sample times (hr)						
Subject #	Predose	0.08	0.17	0.25	0.33	0.42	0.5
5							
9							
28							
31							

Table 3. Corrected Plasma Glucose Concentrations (pg/mL) following Drug A or Drug B

	Sample times (hr)						
Subject #	Predose	0.08	0.17	0.25	0.33	0.42	0.5
5							
9							
28							
31							

Table 4. Corrected Plasma Glucagon Concentrations (pg/mL) following Drug A or Drug B

	Sample times (hr)						
Subject #	Predose	0.08	0.17	0.25	0.33	0.42	0.5

5							
9							
28							
31							

Please confirm receipt of this request and provide an anticipated timeframe for your response.

Regards,

Elisabeth A. Hanan, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

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ELISABETH A HANAN
01/13/2015



NDA 201849

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Fresenius Kabi USA, LLC
Attention: Jeremy Rybicki
Manager, Regulatory Affairs
Three Corporate Drive
Lake Zurich, Illinois 60047

Dear Mr. Rybicki:

Please refer to your New Drug Application (NDA) dated August 8, 2014, received August 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for glucagon for injection.

On December 19, 2014, we received your December 19, 2014, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **May 8, 2015**.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by **April 8, 2015**.

If you have any questions, call Elisabeth Hanan, Regulatory Project Manager, at (240) 402-0350.

Sincerely,

{See appended electronic signature page}

Julie Van der Waag
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELISABETH A HANAN

01/07/2015

on behalf of J. Van der Waag

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (glucagon) Information Request
Date: Tuesday, December 30, 2014 1:07:22 PM

Good afternoon,

Regarding your NDA resubmitted on August 8, 2014, for glucagon for injection, we have the following information request:

In our review of treatment emergent adverse events (TEAEs) reported in your NDA we have noted the following:

1. Sometimes the table of contents of the CRFs did not list individual TEAEs that were described inside the CRF; therefore had we looked at the table of contents only we would have missed the actual TEAE.
2. We added up each of the individual AEs and reached a total number of TEAEs that does not match the number reported by you in the Clinical Study Report (ref Clinical Study Report No AA98483 page 38). You report 185 TEAEs in 31 subjects; we get a slightly higher number.

We ask that you confirm that a total of 185 TEAEs were experienced by 31 subjects as you stated in Clinical Study Report No AA98483 page 38, or provide corrected information.

Please confirm receipt of this request and provide an anticipated timeframe for your response.

Regards,

Elisabeth A. Hanan, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

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ELISABETH A HANAN
12/30/2014

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 Carton/Container Labeling
Date: Tuesday, November 04, 2014 2:55:02 PM

Good afternoon,

Regarding your proposed carton and container labeling submitted on August 8, 2014, our review team has the following comment:

Revise the NDC number of the vial to one which differs from that on the carton labeling.

We request that you submit revised labeling that incorporates this change by November 26, 2014.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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ELISABETH A HANAN
11/04/2014

From: [Hanan, Elisabeth](mailto:Hanan.Elisabeth@fresenius-kabi.com)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 Information Request
Date: Tuesday, October 21, 2014 4:14:37 PM

Good afternoon,

Reference is made to your submission dated September 18, 2014, to NDA 201849 (glucagon for injection), which included the Source Case Report forms from clinical study GLUC-002-CP1 entitled "Bioequivalence of a Test Formulation of Glucagon for SC Injection Compared to Glucagon for Injection (Bedford Laboratories) Under Fasted Conditions." Reference is also made to the synopsis of study GLUC-002-CP1 submitted on August 8, 2014.

There are discrepancies in the test and reference product Lot numbers and expiration dates in the above two submissions. The case report forms also indicate that the drug was administered intravenously to the subjects.

The information included in the synopsis of clinical study GLUC-002-CP1 (submission dated August 8, 2014) is as follows:

"Test Product: 1 mg (1 IU/mL) Glucagon for Injection (Fresenius Kabi USA), (Lot No: C113-002, Expiration Date: April 2015).

Reference Product: 1 mg (1 IU/mL) of GlucaGen® (Bedford Laboratories), (Lot No: BW60511, Expiration Date: April 2014)."

The information included in the Case Report Forms in submission dated September 18, 2014, is included below:

"Test Product: 1 mg (1 IU/mL) Glucagon for injection (Synthetic) (APP Pharmaceuticals), Lot No.: C109-002. Expiration Date: 01 /2010, administered intravenously preceded by an overnight fast of 10 hours.

Reference Product: 1 mg (1 IU/mL) of Glucagon for Injection (rDNA origin) (Bedford Laboratories), Lot No.: vw60516, Expiration Date: 09/2010, administered intravenously preceded by an overnight fast of 10 hours."

Address the above discrepancies. We request that you provide a response by close of business on October 28, 2014. You may submit your response to me by email for rapid distribution to the team, but a formal submission to the NDA file will also be required.

Please confirm receipt of this email and let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

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/s/

ELISABETH A HANAN
10/21/2014

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (glucagon) Preliminary Labeling Comments
Date: Thursday, September 18, 2014 3:08:18 PM
Attachments: [Glucagon NDA 201849 Preliminary Labeling Comments 18Sep2014.doc](#)

Good afternoon,

During our preliminary review of the labeling submitted to this NDA on August 8, 2014, we have identified several labeling issues as indicated in the attached document. Note that your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website. We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by November 1, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist (available at the website linked above) to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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ELISABETH A HANAN
09/18/2014

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (glucagon for injection) Information Request
Date: Wednesday, September 10, 2014 3:08:41 PM

Good afternoon,

I have the following information request from our review team:

Submit the bioanalytical report(s) for glucose and glucagon sample analysis performed under Protocol No. GLUC-002-CP1, or specify where they can be found in your submission received on August 8, 2014.

You may submit your responses to me by email for rapid distribution to the team; however, the responses must also be submitted as a formal amendment to the NDA file.

Please let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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/s/

ELISABETH A HANAN
09/10/2014

From: [Hanan, Elisabeth](#)
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: RE: NDA 201849 (glucagon for injection) Information Request
Date: Friday, August 22, 2014 2:20:48 PM

Good afternoon,

I received two additional information requests as follows:

Regarding Protocol No. GLUC-002-CP1, *Bioequivalence of a Test Formulation of Glucagon for SC Injection Compared to Glucagon for Injection (Bedford Laboratories) Under Fasted Conditions*:

1. Submit all Case Report Forms.
2. If available, please re-submit a copy of the study protocol in a file format that can be searched

Please confirm receipt of these information requests and let me know if you have questions.

Thank you,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

From: Hanan, Elisabeth
Sent: Friday, August 22, 2014 12:10 PM
To: Jeremy.Rybicki@fresenius-kabi.com
Subject: NDA 201849 (glucagon for injection) Information Request

Good afternoon,

I have the following information request from our review team:

We are not able to locate the bioanalytical method and validation study reports for both glucagon and glucose for the study GLUC-002-CP1 in your NDA resubmission dated August 8, 2014. Please submit this information or let us know of its location in the current submission. Also provide information on the site where the bioanalytical portion of the study was conducted. Send your responses by COB August 22, 2014.

You may submit your responses to me by email for rapid distribution to the team; however, the

responses must also be submitted as a formal amendment to the NDA file.

Please let me know if you have any questions.

Regards,

Elisabeth A. Hanan, M.S.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

elisabeth.hanan@fda.hhs.gov

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/s/

ELISABETH A HANAN
08/22/2014



NDA 201849

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Fresenius Kabi USA, LLC
Attention: Jeremy Rybicki
Manager, Regulatory Affairs
Three Corporate Drive
Lake Zurich, Illinois 60047

Dear Mr. Rybicki:

We acknowledge receipt on August 8, 2014, of your August 8, 2014, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for glucagon for injection.

We consider this a complete, class 2 response to our September 27, 2012, action letter. Therefore, the user fee goal date is February 8, 2015.

If you have any questions, call me at (240) 402-0350.

Sincerely,

{See appended electronic signature page}

Elisabeth A. Hanan, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELISABETH A HANAN
08/20/2014



NDA 201849

MEETING MINUTES

Fresenius Kabi USA, LLC.
Attention: Heidi Guzalo, Ph.D.
Senior Manager, Regulatory Affairs
1501 E. Woodfield Road, Suite 300 East
Schaumburg, IL 60173

Dear Dr. Guzalo:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Glucagon for Injection.

We also refer to the teleconference between representatives of your firm and the FDA on November 27, 2012. The purpose of the meeting was to discuss deficiencies listed in the complete response letter dated September 27, 2012.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Post Action Meeting

Meeting Date and Time: November 27, 2012 from 2:00 pm to 3:00 pm
Meeting Location: Teleconference

Application Number: 201849
Product Name: Glucagon for Injection
Indication: Indicated for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract

Sponsor/Applicant Name: Fresenius Kabi USA, LLC.

Meeting Chair: Mary Parks, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

CDER ATTENDEES:

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D., Division Director
Meghna M. Jairath, Pharm.D., Regulatory Project Manager
Pam Lucarelli, Acting Chief, Project Management Staff
Karim Calis, M.D., Clinical Reviewer
Lisa Yanoff, M.D., Acting Clinical Team Leader
Karen Davis-Bruno, Ph.D., Non-Clinical Supervisor
Indra Antonipillai, Ph.D., Non-Clinical Reviewer

Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)

Jaya Vaidyanathan, Ph.D., Clinical Pharmacology Reviewer
Lokesh Jain, Ph.D., Clinical Pharmacology Team Leader

Office of Compliance, Office of Manufacturing and Product Quality OMPQ

Steve Hertz, Consumer Safety Officer

SPONSOR ATTENDEES:

Chris Bryant, Chief Scientific Officer
David Bowman, VP of Innovation and Development
Jeremy Rybicki, Manager, Regulatory Affairs
Maria Guseva, Scientific Research Associate
Molly Rapp, VP of Regulatory Affairs

1.0 BACKGROUND

Sponsor submitted this 505(b)(2) NDA on October 5, 2010, for Glucagon for injection in use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract. FDA issued a Complete Response (CR) letter on September 27, 2012, due to deficiencies in clinical pharmacology and facility.

Sponsor submitted a post-action Type A meeting request on October 5, 2012, to discuss the deficiencies listed in the CR letter issued by FDA.

FDA granted the teleconference on November 16, 2012 but the sponsor submitted additional information for review via email on November 11, 2012. In order to review the additional information, meeting was rescheduled for November 27, 2012.

Sponsor did not submit a background package and the questions repeated below were included in the meeting request. FDA did not send any preliminary comments to the sponsor. The meeting discussion is in **bold**.

2.0 Sponsor Questions

Sponsor Question 1: Clinical Pharmacology - FK USA would like to understand the Agency's concerns regarding the PD measurements of Glucose analyte measured in the pivotal Bioequivalency Study 200090101. FK USA was able to demonstrate PK values were clinically Bioequivalent to the GlucaGen recombinant product currently on the market.

Meeting Discussion: The Sponsor discussed their rationale (as provided to the Agency in the 11 Nov email) for why only PK data (i.e. not PD data) should be needed to support the diagnostic indication for glucagon, in particular, that literature published to date indicates that the mechanism of action for diagnostic vs. hypoglycemic indications for glucagon are not related, and that blood glucose measurements are not performed during diagnostic use of glucagon for radiologic examinations.

FDA raised the following concerns:

1. Based on publications that the Sponsor provided and FDA's own literature search with regard to the mechanism of action, it is not entirely clear that glucagon's effect on GI motility is independent of its effect on glucose levels. The reviewed publications do not suggest a clear direct relationship between glucose and glucagon measurements. Therefore, both Pharmacokinetic (PK) and Pharmacodynamic (PD) parameters should be included in the bioequivalence (BE) study.

2. FDA is concerned about off-label use of the product and believes that labeling and distribution planning cannot completely ensure that the product would not be used for the hypoglycemia indication. FDA stated that, therefore, our preference is for the Sponsor to evaluate the glucagon product's PD effect on glucose even if the glucagon product is marketed only for the diagnostic indication.

3. FDA noted the regulatory precedent for the development of glucagon products, and pointed out that the currently approved glucagon products have evaluated both PK and PD parameters.

4. FDA stated that removing the PD requirement from this NDA could result in potential regulatory complications. For example, if FDA were to approve this product with only the diagnostic indication and then the sponsor were to perform another PK/PD comparability study for the hypoglycemia indication and that study were to fail.

Therefore, FDA expects both PK and PD be evaluated regardless of the proposed indication. Since a repeat PK/PD study will be the pivotal study to support approval, both the PK and PD data should comply with the current bioanalytical standards.

(b) (4)
[REDACTED]
[REDACTED] but that the BE study to support the diagnostic indication would need both PK and PD parameters.

The Sponsor inquired about conducting the required PD study post approval as a Post Marketing Commitment (PMC). FDA stated that such an approach would not be acceptable, and the glucose PD data will be needed to support efficacy claim. PMRs are generally reserved for addressing safety and labeling issues.

Following this discussion, the sponsor agreed to conduct a new BE study for their glucagon product (b) (4) use as a diagnostic aid. The Sponsor proposed to conduct the new BE study for only the subcutaneous route with evaluation of both PK and PD parameters, and inquired whether it would be acceptable to Agency if the intramuscular route is not further evaluated since it was previously studied. FDA stated that this plan appeared reasonable but recommended that the sponsor submit their BE study protocol and overall development plan to the Agency for review before conducting the study. FDA informed the Sponsor that they will need to open an IND to conduct any clinical studies with their investigational product in the U.S. The Sponsor was advised to submit their proposed BE protocol to the IND.

Sponsor Question 2: Facility -Presently, FK USA has indicated its desire to seek only the diagnostic indication (b) (4) Glucagon for Injection and

therefore would not be offering a Sterile Water for injection vial for reconstitution (manufactured at the Grand Island facility). Under these circumstances, does the Agency concur that the compliance status has no bearing on FK USA's ability to obtain approval for its Glucagon for Injection drug product, which is manufactured at its Melrose Park, IL manufacturing facility?

Meeting Discussion: FDA stated that the inclusion of the Grand Island facility in the application with its current compliance issue would be a review issue. The sponsor stated they will no longer list the Grand Island facility manufacturing site when resubmitting the NDA application on from 356h. FDA had no further comments.

Sponsor Question 3: Safety – The Agency has requested a Safety Update that should include all data from nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level. FK USA has not conducted any clinical trials and therefore would approach using a literature review. FK USA would like to obtain agreement that this information, if applicable, may be generated from the time of the Sequence 0007 Resubmission (30 November 2011) up until a date just prior to FK USA's response to the Complete Response Letter.

Meeting Discussion: FDA clarified that comments listed in the CR letter are standard language requiring sponsors to submit an updated literature review for safety data. The literature search should include any safety information available, regardless of indication. FDA requested that the Sponsor include the abstracts from their literature search. It was agreed that the submitted literature review would include literature published from the time when the NDA was originally filed on November 2011 to a future date near the time anticipated for the NDA resubmission.

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/s/

PAMELA LUCARELLI

12/27/2012

P. Lucarelli signing for M. Jairath



NDA 201849

**ACKNOWLEDGE CORPORATE
NAME CHANGE**

Fresenius Kabi USA, LLC.
Attention: Heidi Guzalo
Senior Manager, Regulatory Affairs
1501 E Woodfield Road, Suite 300 East
Schaumburg, IL 60173

Dear Ms. Heidi Guzalo:

We refer to your correspondence dated September 12, 2012, and received September 12, 2012, notifying the Food and Drug Administration (FDA) that the corporate name has been changed from

APP PHARMECUTICALS, LLC.

to

FRESENIUS KABI USA, LLC.

for the following new drug application (NDA):

NDA 201849 for Glucagon for injection.

We have revised our records to reflect this change.

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their DMFs and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEGHNA M JAIRATH
09/24/2012



NDA 201849

INFORMATION REQUEST

APP Pharmaceuticals, LLC
Attention: Heidi Guzalo, Ph.D.
Sr. Manager, Regulatory Affairs
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Dr. Guzalo:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Glucagon for Injection, 1mg/ml, sterile lyophilized powder, intravenous and intramuscular.

We also refer to your May 18, 2012 submission, containing a response to the 74- day letter we issued on February 10, 2012.

We have the following comments and information request. We request a prompt written response within 30 days from the receipt of this letter in order to continue our evaluation of your NDA.

We continue to have a medication error concern with your proposed product. We are concerned that medication errors may arise with the introduction of your product, because you have decided not to pursue the indication for severe hypoglycemia. We have this concern, because the other Glucagon products on the market have been marketed for a considerable length of time for both diagnostic and severe hypoglycemia indications. Therefore patients or healthcare practitioners may also attempt to use your product for the severe hypoglycemia indication. If practitioners or patients attempt to do so in an emergent situation, errors may occur because your product will not have been approved for this use and will not have labeling to guide users on the appropriate use of this product in the emergency situation of severe hypoglycemia. In addition, your glucagon presentation does not contain all the necessary supplies for a patient to be able to prepare and administer the reconstituted product in an emergency setting, potentially leading to a life-threatening or fatal outcome.

You have not adequately mitigated the error concerns that we continue to have for your product. The statement [REDACTED] ^{(b) (4)} does not adequately address these concerns, as it does not explicitly describe the limited indication for your product relative to the indications for other glucagon products, and is frequently overlooked as a deterrent to distribution in locations other than an institutional setting.

In light of our concern, we ask that you improve the measures you propose to prevent the inadvertent dispensing of your products to patients or caregivers for the emergent treatment of hypoglycemia. To that end, we ask that you consider the following:

1. Improved statements and warning on the carton, container, and in your proposed insert labeling.

On the carton and container, these statements should have considerable prominence (e.g. using large bolded font, boxing, color or other means) to alert healthcare providers, patients, and caregivers that the intended use is for diagnostic purposes only (e.g. FOR DIAGNOSTIC USE ONLY), and further warn that the product is not approved for the emergency treatment of hypoglycemia.

Edited Example below to illustrate our thinking (Further comments may result from full review):



2. To further distinguish your product from other available glucagon products, we again recommend you pursue a proprietary name for your proposed product.

We require a minimum of 90 days to review proprietary name proposals for an NDA. Please consider this review timeline as the Prescription Drug User Fee Act (PDUFA) goal date for this application is September 28, 2012. A late submission of a proprietary name may adversely affect the review outcome of this application.

We refer you to the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.

We further refer to the teleconference between APP and FDA on June 1, 2012, in which we discussed our concerns stated above. We have additional comments listed below.

3. You have indicated that you intend only to market your product in 10-unit packs to further mitigate the risk for inadvertent use to treat emergent hypoglycemia. In the future, if you intend to market your product in single-use packaging, please submit in a Prior-Approval-Supplement any packaging and labeling for a single-use product for our review.
4. Please submit your proposed marketing plan and distribution channels for your product.
5. Distributing directly to settings that perform diagnostic procedures or wholesalers that service inpatient facilities may be prudent given that you are requesting approval for only the diagnostic use for this product.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
06/07/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 1, 2012
TIME: 11:30 a.m. to 12:00 p.m.
LOCATION: Teleconference
APPLICATION: NDA 201849
DRUG NAME: Glucagon (synthetic) for injection intramuscular and intravenous
TYPE OF MEETING: Guidance Meeting at FDA request

MEETING CHAIR: Kellie Taylor, Pharm.D., MPH
Mary Parks, M.D.

MEETING RECORDER: Meghna M. Jairath, Pharm.D.

FDA ATTENDEES:

CDER

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D., Division Director

Meghna M. Jairath, Pharm.D., Regulatory Project Manager

Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis (DMEPA)

Kellie Taylor, Pharm.D., MPH, Deputy Director,

Jamie Wilkins Parker, Pharm.D., Acting Team Leader

Office of Chief Counsel

Maryll Toufanian, JD, Associate Chief Counsel for Drugs

EXTERNAL CONSTITUENT ATTENDEES: APP Pharmaceuticals, LLC

Molly Rapp, Vice President, Regulatory Affairs

Dale Carlson, Senior Director, Regulatory Affairs

Jeremy Rybicki, Manager, Regulatory Affairs

Heidi Guzalo, Ph.D., Sr. Manager, Regulatory Affairs

Elizabeth Hartnett, RPh, Director, Vigilance and Medical Affairs

Linda Schulthess, Manager, Regulatory Labeling

BACKGROUND:

APP pharmaceuticals resubmitted this NDA 201849 for Glucagon (synthetic) for injection intramuscular and intravenous on November 30, 2011, after FDA issued a refusal-to-file (RTF) letter on December 8, 2010. APP is seeking an indication of diagnostic use to inhibit GI motility for radiologic exams. APP did not submit a trade name review with their resubmission after RTF.

During the midcycle meeting it was determined that safety concerns for medication errors is present due to the sponsor seeking only an indication for diagnostic use but the product could still be used or dispensed by healthcare providers for the emergent treatment of hypoglycemia which is approved with other available glucagon products. The inadvertent use of this product for treatment of hypoglycemia is particularly concerning as its presentation does not include any syringe, diluent, or labeling to guide the use of the product for emergent administration. FDA also felt that the absence of a trade name will not allow for further distinction between this product and these other approved glucagon products indicated for the treatment of hypoglycemia. FDA further feels that the carton and container that APP submitted for their response to the 74-day letter was inadequate to fully address the concerns communicated to APP in the 74-day filing communication surrounding potential medication errors.

FDA decided that we needed to talk to APP to convey our concerns. DMEP arranged a teleconference with APP on June 1, 2012.

DISCUSSION POINTS:

- APP stated the reason they are pushing back from submitting a trade name is because they are a generic company and are not set up to market trade name product. The company was also concerned that having a trade name now would present problems later (b) (4) The teleconference did not discuss these points further.
- APP stated they will make further changes to the labeling (statements, color, etc..) of the carton and container (C/C). FDA stated that APP's response to the 74-day letter was inadequate and agreed that they need to do additional labeling changes on C/C.
- APP proposed that they will not make the single unit kit and only market the 10-pack of vials in order to further mitigate FDA's concern. This might decrease the likelihood that APP's product will be ordered for use as an emergency treatment for hypoglycemia, and FDA encouraged them to pursue only the 10 pack configuration.
- FDA further stated the purpose of this call was to convey the inadequacy of the labeling proposed to address the risk of errors that we have identified so far in the review. The changes APP outlined on the call (addition of the statement (b) (4) to the principal display panel of the labels and labeling, addition of labeling and warnings to the top panel of the carton, and submission of their planned marketing and distribution channels to the FDA prior to approval) sound reasonable but if they plan to submit a trade name (TN), this would be a separate submission with a 90-day review clock.
- APP inquired how does having a TN prevent dispensing error for hypoglycemia? APP further inquired how does having TN prevent medication errors when a pharmacist pulls up a drug for dispensing and all the other approved glucagon products come up too? FDA acknowledge that a TN would not fully prevent dispensing errors with this product,

But stated that a TN is linked to a specific product and therefore it may reduce the potential for errors in cases if the TN is used when prescribers and clinicians are ordering this specific product. FDA further stated that having all the other proposed labeling measures in place would be needed to further reduce the potential for errors.

FDA inquired what is APP's plan for distribution of their product. (b) (4)

- FDA stated that they will issue an information request letter indicating all our comments discussed and request APP to respond within 30 days of receiving the letter. APP agreed to the 30 day timeline and stated that they will submit their planned marketing and distribution channels to the FDA within the specified time-frame in the information request letter.

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MEGHNA M JAIRATH
06/07/2012

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Wednesday, June 06, 2012 10:21 AM
To: 'hguzalo@APPpharma.com'
Subject: Information Request for NDA 201849 dated 6/6/2012

Dear Ms. Guzalo

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 201849 for Glucagon for Injection. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

1. In section P.1, your "Component Composition per Unit Dose" table is annotated with the comment that, "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." Confirm that the stability batches with the "S" suffix and clinical batches of the same name were manufactured during the same run. Clarify why the suffix was necessary to differentiate the clinical and stability batches
2. Provide a written concurrence to the following agreement: As manufacturing experience is gained, tighten release and stability specifications for individual impurities, total glucagon related impurities, total lactose related impurities, assay by HPLC, and mass balance to reflect your manufacturing capability. RE-evaluation of specifications should occur after the 10th commercial batch.
3. Your drug substance specification for (b) (4) of no more than (b) (4) % is not supported by your toxicology data. Lower this specification to the tested level in the toxicity studies, i.e. no more than (b) (4) %.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you

*Khushboo Sharma, RAC
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270*

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KHUSHBOO SHARMA
06/06/2012

From: [Jairath, Meghna](#)
To: ["Heidi.Guzalo@fresenius-kabi.com"](mailto:Heidi.Guzalo@fresenius-kabi.com)
Subject: IR_Glucagon NDA 201849_Micro
Date: Thursday, May 24, 2012 11:43:49 PM
Importance: High

NDA 201849

Dear Ms. Guzalo:

The following information is being requested by our microbiology reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 201849 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

CDR/CDER/FDA

Attention: DMEP

5901-B Ammendale Road

Beltsville, MD 20705-1266

Respond by: May 31, 2012

Microbiology

FDA Question 1: We note that your drug product manufacturing process includes (b) (4) bioburden samplin (b) (4). Determination of the concentration of your bulk solution bioburden (b) (4) with an accurate understanding of the microbiological quality of your manufacturing process (b) (4). Provide a commitment to perform bioburden samplin (b) (4).

FDA Question 2: Reference is made to the bacterial endotoxins inhibition/enhancement verification study provided in Module 3.2.P.5.3.1.4. We note that only one product lot (R107-002) was tested, and that a statement of endotoxin recovery confirmation (rather than a data set from this testing) was provided in the NDA. Provide data sets from bacterial endotoxins inhibition/enhancement verification testing of three lots of the subject drug product.

Please confirm receipt of this email.

Thanks,

Meghna

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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MEGHNA M JAIRATH
05/24/2012

From: [Jairath, Meghna](#)
To: ["Heidi.Guzalo@fresenius-kabi.com"](mailto:Heidi.Guzalo@fresenius-kabi.com)
Subject: IR_Glucagon NDA 201849_Clin pharm
Date: Tuesday, May 08, 2012 11:02:38 AM
Importance: High

NDA 201849

Dear Ms. Guzalo:

The following information is being requested by our clinical pharmacology reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 201849 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

CDR/CDER/FDA

Attention: DMEP

5901-B Ammendale Road

Beltsville, MD 20705-1266

Respond by: May 11, 2012

1. Submit the bioanalytical report and method validation for the PD marker (glucose determination). If you have already submitted the data, please show us the location in the submission?

Please confirm receipt of this email.

Thanks,
Meghna

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267

Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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MEGHNA M JAIRATH
05/11/2012

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Tuesday, February 21, 2012 2:52 PM
To: 'hguzalo@APPpharma.com'
Subject: Information Request for NDA 201849 dated 2/21/2012

Dear Ms. Guzalo

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 201849 for Glucagon for Injection. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

1. Your acceptance criteria for glucagon related impurities and lactose impurities are not justified by batch records and stability data. Comparison to the reference drug is useful information; however, your manufacturing data demonstrates sufficient control to justify tighter specifications. Tighten these acceptance criteria (in both release and stability specifications) to reflect the data submitted to your NDA.
2. Your drug substance specifications call for no more than $(b)_{(4)}$ % of "any other [*glucagon related*] impurity", but the justification for specifications calls for no more than $(b)_{(4)}$ %. Change your drug substance specification for "any other [*glucagon related*] impurity" to match the specification described in section 3.2.P.4.5.
3. Submit HPLC assay values from method 09-03802 at release and stability (any that is available) for batches C109-002, C108-002, and R107-002. For the stability data provide mass balance calculations for the glucagon and all glucagon related impurities.
4. Amend your release and stability specifications to include:
 - a. HPLC assay determined by HPLC method 09-03802; provide a justification for the proposed acceptance criteria
 - b. mass balance for the glucagon and all glucagon related impurities determined by HPLC method 09-03802; provide a justification for the proposed acceptance criteria
 - c. total lactose related impurities with adequate justification for the proposed acceptance criteria
5. Amend your application by moving the method description for "Instrumental Color of Clear Solutions" (method 08-00848) from section 3.2.P.5.3 (Validation of Analytical Procedures) to section 3.2.P.5.2 (Analytical Procedures).

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you

*Khushboo Sharma, RAC
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270*

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/s/

KHUSHBOO SHARMA
02/21/2012



NDA 201849

FILING COMMUNICATION

APP Pharmaceuticals, LLC
Attention: Heidi Guzalo
Senior Manager, Regulatory Affairs
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Ms. Guzalo:

Please refer to your New Drug Application (NDA) dated November 30, 2011, received November 30, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in response to our December 8, 2011, refusal to file letter, for Glucagon for Injection, 1mg/mL, sterile lyophilized powder, intravenous and intramuscular.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 28, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 7, 2012.

We request that you submit the following information:

1. While it is acceptable to seek only the diagnostic use indication and not the hypoglycemia indication, we encourage you to adequately differentiate your product from the other marketed glucagon products so that patients are not inadvertently given your product for the outpatient treatment of hypoglycemia. Otherwise patients may be severely harmed because your product will not have all the necessary components or labeling to guide users in the appropriate use of this product in the emergency situation of severe hypoglycemia. This risk may not be fully mitigated by your prescribing information labeling. You may wish to consider pursuing a proprietary name as well as differentiating your product through aspects of your product design (such as carton labeling and container labels) and marketing (provider outreach, database alerts and so forth) to help reduce the risk of these errors. Please address this comment at your earliest convenience so that we may consider your measures during the course of your NDA review.

Refer to the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “Pdufa Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.

Please respond only to the above request for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request dated September 30, 2010, received October 5, 2010, for a full waiver of pediatric studies for this application. Since your application does not trigger PREA, you are exempt from this requirement.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
02/10/2012



NDA 201849

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

APP Pharmaceuticals, LLC
Attention: Heidi Guzalo
Sr. Manager, Regulatory Affairs
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Ms. Guzalo:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) in response to our December 8, 2011, refusal to file letter for the following:

Name of Drug Product: Glucagon for Injection, 1mg/ml, sterile lyophilized powder,
intravenous and intramuscular

Date of Application: November 30, 2011

Date of Receipt: November 30, 2011

Our Reference Number: NDA 201849

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 29, 2012, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not

obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEGHNA M JAIRATH
12/09/2011

From: [Jairath, Meghna](#)
To: [Jairath, Meghna;](#)
Subject: FW: FDA response: Glucagon NDA 201849
Date: Monday, June 06, 2011 3:43:27 PM

From: Jairath, Meghna
Sent: Monday, June 06, 2011 3:35 PM
To: 'JRybicki@apppharma.com'
Subject: FDA response: Glucagon NDA 201849

Hello,

See below in regards with your concern about resubmitting the application and if it requires a new NDA #:

- Generally, the sponsor should retain and use their original application number.
- Material already submitted to the application should not be resubmitted. The sponsor should submit new information only. The sponsor should make reference to previously submitted information, but it is not necessary to re-reference each file in the backbone, as this could lead to duplicate entries in Lifecycle view within the eCTD viewer. The sponsor should use lifecycle operators attributes (delete, append, new, replace) to properly designate files submitted in the resubmission sequence.
- Sponsors should code the submission as “resubmission” in the index.xml and relate the sequence back to the “original-application.”

Hope this helps.

Meghna

From: JRybicki@apppharma.com [mailto:JRybicki@apppharma.com]
Sent: Monday, June 06, 2011 12:58 PM

To: Jairath, Meghna
Subject: Glucagon NDA 201849

Dr. Jairath,

In preparation for the response to the FDA's December 3, 2010 REFUSAL TO FILE correspondence for APP's Glucagon for Injection (NDA 201849) I have a few questions that would require some guidance prior to moving forward with our response.

1. Does APP need a new application number to resubmit this drug product to the Agency? [If yes, please disregard questions 2 and 3]
2. If a new application number is not required, this submission will be a sequence to NDA 201849. Does APP need to resubmit all the CTD sections (just as we would in an original submission) or just the sections that have been revised to address the RTF correspondence mentioned above?
3. When we respond, should we use "Amendment" or "Resubmit" as the submission type?

Any information and guidance you can provide is greatly appreciated. Thank you.

Jeremy Rybicki
Regulatory Affairs
APP Pharmaceuticals, LLC - A Company of the Fresenius Kabi Group
1501 E. Woodfield Rd.
Schaumburg, IL 60173
847-969-4896

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/s/

MEGHNA M JAIRATH
06/10/2011



NDA 201849

MEETING MINUTES

APP Pharmaceuticals, LLC
Attention: Jeremy Rybicki
Sr. Regulatory Scientist
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Mr. Rybicki:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucagon for Injection ((b)(4) intramuscular and intravenous).

We also refer to the meeting between representatives of your firm and the FDA on March 3, 2011. The purpose of the meeting was to discuss the FDA's refusal to file action.

A copy of the official minutes of the March 3, 2011, meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Post Refuse to File Informal Conference

Meeting Date and Time: March 3, 2011 from 3:00 pm to 4:00 pm
Meeting Location: FDA White Oak Campus
10903 New Hampshire Avenue
Silver Spring, Maryland, 20993

Application Number: NDA 201849
Product Name: Glucagon injection ((b) (4) intramuscular,
and intravenous)
Indications: (b) (4)
(2.) Use as a diagnostic aid during radiologic
examinations to temporarily inhibit movement of the
gastrointestinal tract

Sponsor/Applicant Name: APP Pharmaceuticals, LLC

Meeting Chair: Mary Parks, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D., Division Director
Meghna M. Jairath, Pharm.D., Regulatory Project Manager
Enid Galliers, Chief, Project Management Staff
Karim Anton Calis, Pharm.D., M.P.H., Primary Medical Reviewer
Hylton Joffe, M.D. M.M.Sc., Medical Team Leader
Karen Davis-Bruno, Ph.D., Pharmacology/Toxicology Team Leader
Indra Antonipillai, Ph.D., Pharmacology/Toxicology Reviewer

**Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology
(OCP), Office of Translational Sciences (OTS)**

Sally Choe, Ph.D., Team leader
Manoj Khurana, Ph.D., Clinical Pharmacology Reviewer

Division of New Drug Assessment III, Office of New Drug Quality Assessment (ONDQA)

Suong (Su) Tran, Ph.D., Chemistry, Manufacturing and Control Lead, Division III

Office of Surveillance and Epidemiology, Division of Pharmacovigilance (DPV) 1

Debra Ryan, Pharm.D., MBA, Safety Evaluator

SPONSOR ATTENDEES

APP Pharmaceuticals Participants:

Christopher Bryant, Ph.D., Executive Vice President and Chief Scientific Officer

David Bowman, Vice President, Product Development

Surendera Tyagi, Vice President, Oncology Business Unit

Toni Glinsey, M.S., RQC, Manager, Regulatory Affairs

External Consultants from (b) (4)

(b) (4)

1.0 BACKGROUND

NDA 201849 was submitted by APP Pharmaceuticals as a 505(b)(2) application for Glucagon for Injection, 1 mg/vial, as a sterile lyophilized drug product to be administered by (b) (4) intramuscular (im), or intravenous (iv) injection. APP is seeking approval (b) (4) as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract. The APP glucagon product is manufactured by synthetic means and is attempting to rely on the efficacy and safety findings of GlucaGen, manufactured by recombinant means by Novo Nordisk.

FDA issued a refuse to file (RTF) letter on December 8, 2010, based primarily on insufficient nonclinical data. APP submitted a meeting request on December 30, 2010, for an informal conference to discuss FDA's RTF action. The meeting request was granted and scheduled for March 3, 2011. Prior to the meeting, on February 22, 2011, FDA sent its preliminary comments to APP via email. APP responded to those comments on March 2, 2011.

Repeated below in regular text are FDA's RTF comments and APP's response and questions. FDA's preliminary responses are written in bold text and APP's pre-meeting responses follow in regular text. The meeting discussion is highlighted in *italics*.

2. DISCUSSION

2.1 NONCLINICAL

FDA RTF Comment 1: The drug impurities/degradants with limits above 1.0% must be clearly identified and qualified.

APP Response: Table 1 Appendix B presents DP impurities/degradants for three lots of DP (lots, R107-002, C108-002, and C109-002) with limits above 1.0%. Qualification is summarized in the last column of Table 1 Appendix B. For the NDA resubmission, this table will be placed into 3.2.P.5.5 as it summarizes data contained in the Glucagon Related Impurities Report and the Lactose Related Impurities Report that were submitted in the original NDA.

The highlighted data (Lot R107-002) represents a lot manufactured in support of a previously filed ANDA, for which the manufacturing process rendered a lower pH than that for the clinical batches (C108-002 and C109-002). However, the target pH will be revised to simulate the higher pH attained during the manufacture of the clinical lots. Thus, the revised target pH will reflect the data currently being generated for the proposed product, as will future production.

APP Question: Does the FDA concur that Table 1 identifies and qualifies drug impurities/degradants with limits above 1.0%?

FDA Preliminary Response: No, we do not concur that Table 1 qualifies drug impurities or degradants with limits >1%. We refer you to ICHQ3 for the qualification process.

APP Preliminary Response: APP would like to better understand and receive clarification as to the agency's position for acceptable molecular characterization of the impurities in the three lots of APP synthetic DP (lots, R107-002, C108-002, and C109-002) with proposed limits above 1.0% as compared to the biologically produced GlucaGen® and the Glucagon for Injection (Lilly).

APP would propose to provide the bridging information, and the link between the APP drug product and the listed drug by using the current LC-MS technology to generate comparative data between APP's proposed Glucagon for Injection drug product and that of GlucaGen® to identify and qualify those impurities with limits above 1.0%.

Meeting Discussion: *The Division reiterated to APP that they provided no bridging nonclinical data comparing their product to the listed drug GlucaGen® or published literature to support safety.* (b) (4)

APP would need to conduct toxicology and genotoxicity studies. These studies should include in vitro genotoxicity (mutagenicity, clastogenicity) and a multiple-dose toxicity study of a minimum duration of 2 weeks up to 12 weeks, in one species with your proposed drug product and the drug product upon which you intend to rely (as per ICH Q3A and ICH Q3B) with toxicokinetics. An alternate approach is to utilize the completed bioequivalence study and your proposal to use LC-MS technology to show similarity of the degradants/impurities to those of the listed drug. However, this approach could only support a bridge for your product via the intramuscular and intravenous routes (it would not support a bridge for the (b) (4) route of administration because the glucagon products were administered intramuscularly in the bioequivalence study). This would allow APP's application to be filed for the diagnostic indication but whether the content submitted will be adequate to bridge your product to the proposed listed drug will be a review issue.

FDA RTF Comment 2: Provide the data (you may reference section 3.2.P.5.5) that show the comparison of impurities/degradants in your product versus the listed drug relied upon, GlucaGen, (21 CFR 314.54(a)(2) requires information in the nonclinical pharmacology and toxicology section of the 505(b)(2) application in support of the difference between your synthetic product and the recombinant GlucaGen).

APP Response: Table 1 Appendix B presents DP impurities/degradants for three lots of APP synthetic DP (lots, R107-002, C108-002, and C109-002) with limits above 1.0% compared to the GlucaGen® RLD and the generic version of Glucagon for Injection (Lilly).

As per 21 CFR §314.54(a)(2) "...any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application."

Therefore, APP provides a commitment to submit the Module 2 Non-Clinical summary sections (Section 2.4, and Sections 2.6.1 – 2.6.7 of the CTD) by relying on peer-reviewed literature and also provide that information needed to support any differences between the APP synthetic DP

and that of the recombinant RLD DP. Module 4 will contain copies of articles that were relied upon to support the relevant Non-Clinical Summaries.

APP does not intend to qualify the (b) (4) Impurity or the two lactose related impurities (b) (4) with limits > 1.0%, as the observed levels for the impurities do not exceed the levels justified by the reference listed drug product. These data are shown in Table 1 Appendix B.

APP Question: Does the FDA concur that it is acceptable to support the Non-Clinical Module 2 summaries by using peer reviewed literature and that the (b) (4) Impurity and the two lactose related impurities (b) (4) with limits > 1.0% will not require toxicology qualification?

FDA Preliminary Response: We do not agree that (b) (4) present at >1% will not require toxicology qualification. Published literature may be used to support a 505(b)(2) application as justified. We remind you that adequate bridging information is needed to provide a link between your product and any published information or the listed drug upon which you are relying. This information has not been provided in the meeting package.

APP Preliminary Response: Refer to the response to RTF comment 1.

Meeting Discussion: Refer to meeting discussion under RTF comment 1.

FDA RTF Comment 3: If the impurity profile of your synthetic product is not identical to the marketed recombinant GlucaGen, provide qualifying toxicity studies. These studies should include *in vitro* genotoxicity (mutagenicity, clastogenicity) and a toxicity study of a minimum duration of 2 weeks up to 12 weeks in one species with the proposed drug product and listed drug (as per ICH Q3A and ICH Q3B) with toxicokinetics. The toxicity studies should clearly identify target organs of toxicity and no observable adverse effect level (NOAELs).

APP Response: The (b) (4) Impurity as well as the two lactose related impurities (b) (4) with limits > 1.0% should not require qualification. As per ICH-Q3, the observed levels for the impurities do not exceed the level justified by the reference listed drug product. Therefore, APP has no plans to conduct qualifying toxicity studies.

APP Question: Does the FDA concur that no qualifying toxicity studies are required since the impurity levels do not exceed the level justified by the RLD?

FDA Preliminary Response: It is unclear what information you plan to use to provide a bridge between the listed drug and your product; therefore, we cannot agree that toxicology studies will not be needed as outlined in the Refuse-to-file letter.

APP Preliminary Response: Refer to the response to RTF comment 1.

Meeting Discussion: Refer to meeting discussion under RTF comment 1.

2.2 REGULATORY

FDA RTF Comment 4: Submit the required financial disclosure information as per 21 CFR 54.4(c).

APP Response: APP will submit the required financial disclosure information as specified per 21 CFR §54.4(c).

APP Question: Will the addition of a Form FDA 3454 completed and signed by the applicant, in conjunction with the Financial Disclosure Statements previously provided by the Clinical Investigators, be sufficient for this requirement?

FDA Preliminary Response: Your financial disclosure statements have not been reviewed. If your signed Form FDA 3454 covers all investigators who conducted covered clinical studies, it should satisfy the requirements under Part 54 of Title 21 of the CFR.

APP Preliminary Response: No further clarification or discussion is required.

Meeting Discussion: No further discussion.

Following comments are not refuse to file issues but FDA requested feedback.

2.3 CHEMISTRY, MANUFACTURING AND CONTROLS

FDA Comment A: 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.

APP Response: Table 1 Appendix B presents DP impurities/degradants for three lots of APP synthetic DP (lots, R107-002, C108-002, and C109-002) compared to the Glucagen® RLD and the generic version of Glucagon for Injection (Lilly).

Additionally, two sets of comparative chromatograms are provided as attachments in Section 11.3 Appendix C. Set 1 provides chromatographic representation of APP's C109-002 clinical lot stacked against the GlucaGen® RLD and Lilly lots. Set 2 provides chromatographic representation of APP's C109-002, C108-002, and R107-002 lots stacked against the GlucaGen® RLD and Lilly lots. These data will also be provided within the Section 3.2.P.5.5 of the submission.

APP Question: Does the FDA concur that Table 1 Appendix A along with the attached chromatograms in Section 11.3 Appendix C provide an adequate summary of data contained in section 3.2.P.5.5 thereby allowing an adequate comparison of impurities/degradants between the APP synthetic DP and the recombinant GlucaGen® RLD to be made?

FDA Preliminary Response: Although the impurity profiles of the new product and the listed drug upon which you intend to rely qualitatively appear similar, the analytical capability is not sufficient to discern differences that can impact safety of the new product. The levels of impurities have not been assigned to specific, identified impurities in the different products. We cannot conclude from the provided data that specific impurities are present at the same or different levels in comparing the products. Therefore, the analytical comparison cannot support a waiver of required nonclinical studies.

APP Preliminary Response: Refer to the response to RTF comment 1.

Meeting Discussion: The Division agreed that APP's proposal (to use the current LC-MS technology to generate comparative data between APP's proposed Glucagon for Injection and GlucaGen® to identify impurities with limits above 1.0%) is acceptable. These major impurities will be identified by weight and sequence.

FDA Comment B: 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.

APP Response: One of the lactose related impurities is (b) (4). Prior to the NDA resubmission, identification of this impurity will be performed along with RLD to attempt to obtain a putative molecular structure and a specification limit will be set. All the data reported in Table 1 Appendix B are the highest result seen from unstressed conditions.

APP Question: Does the FDA concur with the plans to identify this impurity and specify a DP limit?

FDA Preliminary Response: Your plan is adequate for quality control purposes. Refer to the nonclinical comments regarding the qualification requirement for any impurity limit higher than 1.0%.

APP Preliminary Response: No further clarification or discussion is required.

Meeting Discussion: No further discussion.

FDA Comment C: 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.

APP Response: Reference is made to section 3.2.P.2.2.1.1 and the Light Sensitivity Study contained therein. From this study it was concluded that (b) (4).

(b) (4)

Reference is made to section 3.2.P.3.3.1.1 -

(b) (4)

Photostability data for the lyophilized DP and the reconstituted DB/bulk solution will be provided in the NDA resubmission. The reconstituted drug product is the same composition as the bulk solution.

APP Question: Does the FDA concur with the plans to submit photostability data for the lyophilized DP and the light sensitivity study for the bulk solution?

FDA Preliminary Response: Yes, we concur with your plan to submit photostability data for the lyophilized drug product and light sensitivity study for the bulk solution.

APP Preliminary Response: No further clarification or discussion is required.

Meeting Discussion: No further discussion.

2.4 CLINICAL

FDA Comment D: Data sets for the bioequivalence (BE) study were not provided. Submit datasets that include patient identifiers and all measured safety parameters.

APP Response: Adverse events (AEs) were collected and a tabular summary was provided for the BE study No 20090101. Unfortunately, the statistical analyses of these safety data (datasets) were inadvertently omitted from the submission. However, these datasets are available and do include identifiers and all measured safety parameters. These datasets will be provided in the resubmission.

A total of 24 adverse events (13, Test Product; 11, Reference Product) were reported by 12 of the 32 subjects who participated in this BE study. Twenty-three of the adverse events were considered "mild", of these, 22 resolved spontaneously prior to study completion and one resolved with treatment. One adverse event was considered "moderate" and had not resolved by the end of the study. The most frequent adverse events reported for the test product were nausea (5 subjects) and vomiting (2 subjects). The most frequent adverse events reported for the reference product were nausea (4 subjects) and vomiting (2 subjects).

A data listing and summary of all adverse events that includes patient identifiers can be found in Section 11.4 Appendix D of this response and these data were located in section 5.3.1.2 of the original NDA submission. A tabular summary of the frequency of AEs by body system is also provided in Section 11.4 Appendix D of this response.

APP Question: Does the FDA concur that provision of the (SAS) data sets including the measured safety parameters for this study and that the submitted adverse events subject listings

and tabular summary of AEs by body system will be adequate to characterize the safety data that is currently available?

FDA Preliminary Response: We understand that you plan to include the requested bioequivalence (BE) study data sets with your resubmission. We also understand that you plan to include participant identifiers and all measured safety parameters. For the clinical safety data, our preference is to receive them in SDTM and ADaM format (CDISC). Until we review these data we cannot comment on their overall adequacy. Also, we note that the BE study was conducted with 32 participants but only 25 completed the study. A detailed explanation for the 7 dropouts should be provided in the NDA.

APP Preliminary Response: Subject narratives will be prepared for all dropouts.

Meeting Discussion: No further discussion.

FDA Comment E: You are proposing the use of your product [REDACTED] (b) (4) for use as a diagnostic aid. The proposed commercial product as described in your application is to be supplied as [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

2.5 CLINICAL PHARMACOLOGY

FDA Comment F: Provide raw concentration data, the pharmacokinetic (PK) dataset for glucagon and the pharmacodynamic (PD) dataset for glucose (as SAS transport files) for the bioequivalence trial-Study No. 20090101.

- The concentration dataset should at a minimum have the following columns: ID, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence.
- The PK and PD parameter datasets should at a minimum have the following columns: ID, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence. Provide baseline uncorrected as well as baseline corrected PD data in separate files.

- Include any other relevant information in these datasets that in your thinking could help us efficiently review your application.

APP Response: APP apologizes for inadvertently omitting the SAS datasets from the original submission. The XPORT dataset includes the following four files and these will be included in the NDA resubmission in the appropriate Module 5 subfolder:

1) Raw, 2) PK, 3) Ke, and 4) Time

The record layout of these files is fully explained in define (readme.pdf) files included in the dataset export files within the datasets folder. These datasets encompass all of the information required by the FDA. Additionally, the datasets presented in the statistical methods file within the report are presented in the format requested by the Agency.

APP Question: Does the FDA concur that the SAS datasets, as outlined in this response, are sufficient to allow a substantive review of the data derived from the BE Study No. 20090101?

FDA Preliminary Response: Yes, we concur.

APP Preliminary Response: No further clarification or discussion is required.

Meeting Discussion: No further discussion.

FDA Comment G: You are proposing intramuscular, (b) (4) and intravenous routes of administration for your product. However, your pivotal BE study only obtained data for the intramuscular route of administration (b) (4)

(b) (4)

(b) (4)

(b) (4)

Meeting Discussion:

(b) (4)

For the diagnostic indication, GlucaGen is approved for the intramuscular and intravenous routes of administration only. Therefore, the Division agreed that it would consider an application from APP for only the intravenous and intramuscular routes of administration if the application were for diagnostic use only.

(b) (4)

FDA Comment H: Clarify the following discrepancies noted in your submission:

- Under Section 11.1 you indicate that “*For bioequivalence analysis (corrected glucagon data)*” was used. However, the primary PK comparison was based on nonbaseline corrected glucagon data.
- Section 9.7.1 in the Study Protocol (Study No. 20090101, 12/16/08) mentioned that “Primary determination of bioequivalence will be based on the baseline adjusted glucagon results. The uncorrected glucagon analysis and both sets of glucose analysis will be used as supporting evidence”. This is not concordant with the use of uncorrected glucagon PK parameters as the primary comparison in your study reports. No justification was provided for this deviation.
- In Section 14.2 Efficacy Data you mentioned “*Mean concentration versus time plots (linear and ln-linear) are presented below for both baseline-corrected and baseline-uncorrected glucagon and glucose*” but only non-baseline corrected glucagon is presented.

APP Response: APP apologizes for the typographical error cited above. The correct statement should read "non-corrected glucagon". The report will be corrected for the NDA resubmission.

As Glucagon is an endogenous hormone, it is expected to have some physiological baseline concentration in blood. This was the main reason why two sets of analyses were proposed in the study protocol. However, the analytical method used for determining the concentration of Glucagon in blood did not detect any pre-dose concentrations at the lower limit of quantification and therefore all of the concentrations at baseline were zero. As all the pre-dose concentrations had values of zero, baseline-corrected data were unnecessary and not applicable. For that reason only uncorrected glucagon PK analysis is presented, as a corrected data from baseline analysis would be essentially identical to the uncorrected data.

APP Question: Does the FDA concur that corrected base line data is not required, as the data is identical for both baseline-corrected and baseline uncorrected glucagon and glucose?

FDA Preliminary Response: We acknowledge your clarification. We agree that analyses based on baseline-corrected and uncorrected data will be identical if the baseline concentrations are zero. However, you should include a clear justification for this deviation from the originally planned primary comparison in your study report.

APP Preliminary Response: The clinical study report will be amended to include this correction and justification for the deviation.

Meeting Discussion: No further discussion.

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/s/

MEGHNA M JAIRATH
03/24/2011



NDA 201849

MEETING PRELIMINARY COMMENTS

APP Pharmaceuticals, LLC
Attention: Pajjit Ostrowski
Regulatory Scientist
1501 East Woodfield Road Suite 300E
Schaumburg, Illinois 60173

Dear Ms.Ostrowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Glucagon for Injection ((b) (4) intramuscular, and intravenous).

We also refer to your December 30, 2011, correspondence, received December 30, 2011, requesting an informal conference meeting to discuss our refuse-to-file decision.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 3, 2011, 3:00 pm to 4:00 pm, 10903 New Hampshire Avenue, White Oak Building 22, Conference Room 1313, Silver Spring, Maryland, 20993, between APP Pharmaceuticals and the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of contacting me to cancel the meeting. If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

FDA's RTF Comments, Sponsor's Questions and FDA's Preliminary Responses

NONCLINICAL

FDA RTF Comment 1: The drug impurities/degradants with limits above 1.0% must be clearly identified and qualified.

Sponsor Response: Table 1 Appendix B presents DP impurities/degradants for three lots of DP (lots, R107-002, C108-002, and C109-002) with limits above 1.0%. Qualification is summarized in the last column of Table 1 Appendix B. For the NDA resubmission, this table will be placed into 3.2.P.5.5 as it summarizes data contained in the Glucagon Related Impurities Report and the Lactose Related Impurities Report that were submitted in the original NDA.

The highlighted data (Lot R107-002) represents a lot manufactured [REDACTED] (b) (4) [REDACTED] for which the manufacturing process rendered a lower pH than that for the clinical batches (C108-002 and C109-002). However, the target pH will be revised to simulate the higher pH attained during the manufacture of the clinical lots. Thus, the revised target pH will reflect the data currently being generated for the proposed product, as will future production.

Sponsor Question: Does the FDA concur that Table 1 identifies and qualifies drug impurities/degradants with limits above 1.0%?

FDA Preliminary Response: No, we do not concur that Table 1 qualifies drug impurities or degradants with limits >1%. We refer you to ICHQ3 for the qualification process.

FDA RTF Comment 2: Provide the data (you may reference section 3.2.P.5.5) that show the comparison of impurities/degradants in your product versus the listed drug relied upon, GlucaGen, (21 CFR 314.54(a)(2) requires information in the nonclinical pharmacology and toxicology section of the 505(b)(2) application in support of the difference between your synthetic product and the recombinant GlucaGen).

Sponsor Response: Table 1 Appendix B presents DP impurities/degradants for three lots of APP synthetic DP (lots, R107-002, C108-002, and C109-002) with limits above 1.0% compared to the Glucagen® RLD and the generic version of Glucagon for Injection (Lilly).

As per 21 CFR §314.54(a)(2) “...any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application.”

Therefore, APP provides a commitment to submit the Module 2 Non-Clinical summary sections (Section 2.4, and Sections 2.6.1 – 2.6.7 of the CTD) by relying on peer-reviewed literature and also provide that information needed to support any differences between the APP synthetic DP

and that of the recombinant RLD DP. Module 4 will contain copies of articles that were relied upon to support the relevant Non-Clinical Summaries.

APP does not intend to qualify the (b) (4) Impurity or the two lactose related impurities (b) (4) with limits > 1.0%, as the observed levels for the impurities do not exceed the levels justified by the reference listed drug product. These data are shown in Table 1 Appendix B.

Sponsor Question: Does the FDA concur that it is acceptable to support the Non-Clinical Module 2 summaries by using peer reviewed literature and that the (b) (4) Impurity and the two lactose related impurities (b) (4) with limits > 1.0% will not require toxicology qualification?

FDA Preliminary Response: We do not agree that (b) (4) present at >1% will not require toxicology qualification. Published literature may be used to support a 505(b)(2) application as justified. We remind you that adequate bridging information is needed to provide a link between your product and any published information or the listed drug upon which you are relying. This information has not been provided in the meeting package.

FDA RTF Comment 3: If the impurity profile of your synthetic product is not identical to the marketed recombinant GlucaGen, provide qualifying toxicity studies. These studies should include *in vitro* genotoxicity (mutagenicity, clastogenicity) and a toxicity study of a minimum duration of 2 weeks up to 12 weeks in one species with the proposed drug product and listed drug (as per ICH Q3A and ICH Q3B) with toxicokinetics. The toxicity studies should clearly identify target organs of toxicity and no observable adverse effect level (NOAELs).

Sponsor Response: The (b) (4) Impurity as well as the two lactose related impurities (b) (4) with limits > 1.0% should not require qualification. As per ICH-Q3, the observed levels for the impurities do not exceed the level justified by the reference listed drug product. Therefore, APP has no plans to conduct qualifying toxicity studies.

Sponsor Question: Does the FDA concur that no qualifying toxicity studies are required since the impurity levels do not exceed the level justified by the RLD?

FDA Preliminary Response: It is unclear what information you plan to use to provide a bridge between the listed drug and your product; therefore, we cannot agree that toxicology studies will not be needed as outlined in the Refuse-to-file letter.

REGULATORY

FDA RTF Comment 4: Submit the required financial disclosure information as per 21 CFR 54.4(c).

Sponsor Response: APP will submit the required financial disclosure information as specified per 21 CFR §54.4(c).

Sponsor Question: Will the addition of a Form FDA 3454 completed and signed by the applicant, in conjunction with the Financial Disclosure Statements previously provided by the Clinical Investigators, be sufficient for this requirement?

FDA Preliminary Response: Your financial disclosure statements have not been reviewed. If your signed Form FDA 3454 covers all investigators who conducted covered clinical studies, it should satisfy the requirements under Part 54 of Title 21 of the CFR.

Following comments are not refuse to file issues but FDA requested feedback.

CHEMISTRY, MANUFACTURING AND CONTROLS

FDA Comment A: 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.

Sponsor Response: Table 1 Appendix B presents DP impurities/degradants for three lots of APP synthetic DP (lots, R107-002, C108-002, and C109-002) compared to the Glucagen® RLD and the generic version of Glucagon for Injection (Lilly).

Additionally, two sets of comparative chromatograms are provided as attachments in Section 11.3 Appendix C. Set 1 provides chromatographic representation of APP's C109-002 clinical lot stacked against the GlucaGen® RLD and Lilly lots. Set 2 provides chromatographic representation of APP's C109-002, C108-002, and R107-002 lots stacked against the GlucaGen® RLD and Lilly lots.

These data will also be provided within the Section 3.2.P.5.5 of the submission.

Sponsor Question: Does the FDA concur that Table 1 Appendix A along with the attached chromatograms in Section 11.3 Appendix C provide an adequate summary of data contained in section 3.2.P.5.5 thereby allowing an adequate comparison of impurities/degradants between the APP synthetic DP and the recombinant GlucaGen® RLD to be made?

FDA Preliminary Response: Although the impurity profiles of the new product and the listed drug upon which you intend to rely qualitatively appear similar, the analytical capability is not sufficient to discern differences that can impact safety of the new product. The levels of impurities have not been assigned to specific, identified impurities in the different products. We cannot conclude from the provided data that specific impurities are present at the same or different levels in comparing the products. Therefore, the analytical comparison cannot support a waiver of required nonclinical studies.

FDA Comment B: 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.

Sponsor Response: One of the lactose related impurities is (b) (4). Prior to the NDA resubmission, identification of this impurity will be performed along with RLD to attempt to obtain a putative molecular structure and a specification limit will be set. All the data reported in Table 1 Appendix B are the highest result seen from unstressed conditions.

Sponsor Question: Does the FDA concur with the plans to identify this impurity and specify a DP limit?

FDA Preliminary Response: Your plan is adequate for quality control purposes. Refer to the nonclinical comments regarding the qualification requirement for any impurity limit higher than 1.0%.

FDA Comment C: 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.

Sponsor Response: Reference is made to section 3.2.P.2.2.1.1 and the Light Sensitivity Study contained therein. From this study it was concluded that (b) (4).

Reference is made to section 3.2.P.3.3.1.1 - (b) (4).

Photostability data for the lyophilized DP and the reconstituted DB/bulk solution will be provided in the NDA resubmission. The reconstituted drug product is the same composition as the bulk solution.

Sponsor Question: Does the FDA concur with the plans to submit photostability data for the lyophilized DP and the light sensitivity study for the bulk solution?

FDA Preliminary Response: Yes, we concur with your plan to submit photostability data for the lyophilized drug product and light sensitivity study for the bulk solution.

CLINICAL

FDA Comment D: Data sets for the bioequivalence (BE) study were not provided. Submit datasets that include patient identifiers and all measured safety parameters.

Sponsor Response: Adverse events (AEs) were collected and a tabular summary was provided for the BE study No 20090101. Unfortunately, the statistical analyses of these safety data (datasets) were inadvertently omitted from the submission. However, these datasets are available

and do include identifiers and all measured safety parameters. These datasets will be provided in the resubmission.

A total of 24 adverse events (13, Test Product; 11, Reference Product) were reported by 12 of the 32 subjects who participated in this BE study. Twenty-three of the adverse events were considered "mild", of these, 22 resolved spontaneously prior to study completion and one resolved with treatment. One adverse event was considered "moderate" and had not resolved by the end of the study. The most frequent adverse events reported for the test product were nausea (5 subjects) and vomiting (2 subjects). The most frequent adverse events reported for the reference product were nausea (4 subjects) and vomiting (2 subjects).

A data listing and summary of all adverse events that includes patient identifiers can be found in Section 11.4 Appendix D of this response and these data were located in section 5.3.1.2 of the original NDA submission. A tabular summary of the frequency of AEs by body system is also provided in Section 11.4 Appendix D of this response.

Sponsor Question: Does the FDA concur that provision of the (SAS) data sets including the measured safety parameters for this study and that the submitted adverse events subject listings and tabular summary of AEs by body system will be adequate to characterize the safety data that is currently available?

FDA Preliminary Response: We understand that you plan to include the requested bioequivalence (BE) study data sets with your resubmission. We also understand that you plan to include participant identifiers and all measured safety parameters. For the clinical safety data, our preference is to receive them in SDTM and ADaM format (CDISC). Until we review these data we cannot comment on their overall adequacy. Also, we note that the BE study was conducted with 32 participants but only 25 completed the study. A detailed explanation for the 7 dropouts should be provided in the NDA.

FDA Comment E: You are proposing the use of your product [REDACTED] (b) (4) for use as a diagnostic aid. The proposed commercial product as described in your application is to be supplied as [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

CLINICAL PHARMACOLOGY

FDA Comment F: Provide raw concentration data, the pharmacokinetic (PK) dataset for glucagon and the pharmacodynamic (PD) dataset for glucose (as SAS transport files) for the bioequivalence trial-Study No. 20090101.

- The concentration dataset should at a minimum have the following columns: ID, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence.
- The PK and PD parameter datasets should at a minimum have the following columns: ID, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence. Provide baseline uncorrected as well as baseline corrected PD data in separate files.
- Include any other relevant information in these datasets that in your thinking could help us efficiently review your application.

Sponsor Response: APP apologizes for inadvertently omitting the SAS datasets from the original submission. The XPORT dataset includes the following four files and these will be included in the NDA resubmission in the appropriate Module 5 subfolder:

1) Raw, 2) PK, 3) Ke, and 4) Time

The record layout of these files is fully explained in define (readme.pdf) files included in the dataset export files within the datasets folder. These datasets encompass all of the information required by the FDA. Additionally, the datasets presented in the statistical methods file within the report are presented in the format requested by the Agency.

Sponsor Question: Does the FDA concur that the SAS datasets, as outlined in this response, are sufficient to allow a substantive review of the data derived from the BE Study No. 20090101?

FDA Preliminary Response: Yes, we concur.

FDA Comment G: You are proposing intramuscular, (b) (4) and intravenous routes of administration for your product. However, your pivotal BE study only obtained data for the intramuscular route of administration (b) (4)



(b) (4)



FDA Comment H: Clarify the following discrepancies noted in your submission:

- Under Section 11.1 you indicate that “*For bioequivalence analysis (corrected glucagon data)*” was used. However, the primary PK comparison was based on nonbaseline corrected glucagon data.
- Section 9.7.1 in the Study Protocol (Study No. 20090101, 12/16/08) mentioned that “Primary determination of bioequivalence will be based on the baseline adjusted glucagon results. The uncorrected glucagon analysis and both sets of glucose analysis will be used as supporting evidence”. This is not concordant with the use of uncorrected glucagon PK parameters as the primary comparison in your study reports. No justification was provided for this deviation.

• In Section 14.2 Efficacy Data you mentioned “*Mean concentration versus time plots (linear and ln-linear) are presented below for both baseline-corrected and baseline-uncorrected glucagon and glucose*” but only non-baseline corrected glucagon is presented.

Sponsor Response: APP apologizes for the typographical error cited above. The correct statement should read "non-corrected glucagon". The report will be corrected for the NDA resubmission.

As Glucagon is an endogenous hormone, it is expected to have some physiological baseline concentration in blood. This was the main reason why two sets of analyses were proposed in the study protocol. However, the analytical method used for determining the concentration of Glucagon in blood did not detect any pre-dose concentrations at the lower limit of quantification and therefore all of the concentrations at baseline were zero. As all the pre-dose concentrations had values of zero, baseline-corrected data were unnecessary and not applicable. For that reason only uncorrected glucagon PK analysis is presented, as a corrected data from baseline analysis would be essentially identical to the uncorrected data.

Sponsor Question: Does the FDA concur that corrected base line data is not required, as the data is identical for both baseline-corrected and baseline uncorrected glucagon and glucose?

FDA Preliminary Response: We acknowledge your clarification. We agree that analyses based on baseline-corrected and uncorrected data will be identical if the baseline concentrations are zero. However, you should include a clear justification for this deviation from the originally planned primary comparison in your study report.

Please provide us with a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEGHNA M JAIRATH
02/22/2011



NDA 201849

**CONFIRM MEETING DATE
RE REFUSAL-TO-FILE**

APP Pharmaceuticals, LLC
Attention: Pajit Ostrowski
Regulatory Scientist
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Ms. Ostrowski:

Please refer to your September 30, 2010 new drug application (NDA) for Glucagon for Injection ((b) (4) intramuscular and intravenous) that was the subject of our December 8, 2010 refusal to file letter.

In response to your December 30, 2010 request under 21 CFR 314.101(a), we have scheduled a meeting for:

Date: Thursday, March 3, 2011

Time: 3:00 pm to 4:00 pm

**Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20993**

CDER Participants:

Office of Drug Evaluation II (ODE II)

Leah W. Ripper, Associate Director for Regulatory Affairs

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D., Division Director

Meghna M. Jairath, Pharm.D., Regulatory Project Manager

Enid Galliers, Chief, Project Management Staff

Karim Calis, M.D., Primary Medical Reviewer

Hylton Joffe, M.D. M.M.Sc., Medical Team Leader

Karen Davis-Bruno, Ph.D., Pharmacology/Toxicology Team Leader

Indra Antonipillai, Ph.D., Pharmacology/Toxicology Reviewer

**Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology (OCP),
Office of Translational Sciences (OTS)**

Sally Choe, Ph.D., Team leader
Manoj Khurana, Ph.D., Clinical Pharmacology Reviewer
Arindam Dashgupta, Ph.D., Bioequivalence Reviewer

Division of New Drug Assessment III, Office of New Drug Quality Assessment (ONDQA)

Suong (Su) Tran, Ph.D., Chemistry, Manufacturing and Control Lead, Division III
Mutukumaram Ramaswamy, Ph.D., Chemistry reviewer
John Metcalfe, Ph.D., Microbiology reviewer

Additional FDA participants will be communicated by email.

Please e-mail me any updates to your attendees at meghna.jairath@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Meghna M. Jairath @ 301-796-4267; Lena Staunton @ 301-796-7522.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 25 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by January 31, 2011, we may cancel or reschedule the meeting.

Submit the 25 desk copies to the address shown below.

If sending via USPS or any other carriers (e.g. UPS, DHL), please send to:

Meghna M. Jairath, Pharm.D.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3387
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely yours,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MEGHNA M JAIRATH

01/14/2011

Signing on behalf of Dr. Mary Parks



NDA 201849

REFUSAL TO FILE

APP Pharmaceuticals, LLC
Attention: Pajit Ostrowski
Regulatory Scientist
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Ms. Ostrowski:

Please refer to your September 30, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucagon for Injection ([REDACTED] (b) (4) intramuscular and intravenous).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Non-Clinical

1. The drug impurities/degradants with limits above 1.0% must be clearly identified and qualified.
2. Provide the data (you may reference section 3.2.P.5.5) that show the comparison of impurities/degradants in your product versus the listed drug relied upon, GlucaGen, (21 CFR 314.54(a)(2) requires information in the nonclinical pharmacology and toxicology section of the 505(b)(2) application in support of the difference between your synthetic product and the recombinant GlucaGen).
3. If the impurity profile of your synthetic product is not identical to the marketed recombinant GlucaGen, provide qualifying toxicity studies. These studies should include *in vitro* genotoxicity (mutagenicity, clastogenicity) and a toxicity study of a minimum duration of 2 weeks up to 12 weeks in one species with the proposed drug product and listed drug (as per ICH Q3A and ICH Q3B) with toxicokinetics. The toxicity studies should clearly identify target organs of toxicity and no observable adverse effect level (NOAELs).

Regulatory

4. Submit the required financial disclosure information as per 21 CFR 54.4(c).

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

We also have the following comments regarding your application that are not refuse to file issues. However, these comments should be addressed in your new submission.

Chemistry, Manufacturing and Controls

- A. 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.
- B. 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.
- C. 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.

Clinical

- D. Data sets for the bioequivalence (BE) study were not provided. Submit datasets that include patient identifiers and all measured safety parameters.
- E. You are proposing the use of your product (b) (4) for use as a diagnostic aid. The proposed commercial product as described in your application is to be supplied as (b) (4)

[Redacted]

Clinical Pharmacology

- F. Provide raw concentration data, the pharmacokinetic (PK) dataset for glucagon and the pharmacodynamic (PD) dataset for glucose (as SAS transport files) for the bioequivalence trial-Study No. 20090101.
- The concentration dataset should at a minimum have the following columns: ID, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence.
 - The PK and PD parameter datasets should at a minimum have the following columns: ID, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence. Provide baseline uncorrected as well as baseline corrected PD data in separate files.
 - Include any other relevant information in these datasets that in your thinking could help us efficiently review your application.
- G. You are proposing intramuscular, (b) (4) and intravenous routes of administration for your product. However, your pivotal BE study only obtained data for the intramuscular route of administration (b) (4)
- H. Clarify the following discrepancies noted in your submission:
- Under Section 11.1 you indicate that “*For bioequivalence analysis (corrected glucagon data)*” was used. However, the primary PK comparison was based on non-baseline corrected glucagon data.
 - Section 9.7.1 in the Study Protocol (Study No. 20090101, 12/16/08) mentioned that “Primary determination of bioequivalence will be based on the baseline adjusted glucagon results. The uncorrected glucagon analysis and both sets of glucose analysis will be used as supporting evidence”. This is not concordant with the use of uncorrected glucagon PK parameters as the primary comparison in your study reports. No justification was provided for this deviation.
 - In Section 14.2 Efficacy Data you mentioned “*Mean concentration versus time plots (linear and ln-linear) are presented below for both baseline-corrected and baseline-uncorrected glucagon and glucose*” but only non-baseline corrected glucagon is presented.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely yours,

/s/ on December 3, 2010

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
12/03/2010



NDA 201849

NDA ACKNOWLEDGMENT

APP Pharmaceuticals, LLC
Attention: Pajjit Ostrowski
Regulatory Scientist
1501 East Woodfield Road Suite 300E
Schaumburg, Illinois 60173

Dear CONTACT:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Glucagon for Injection, 1mg/vial

Date of Application: September 30, 2010

Date of Receipt: October 5, 2010

Our Reference Number: NDA 201849

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 4, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, please call me at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEGHNA M JAIRATH
10/20/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10/14/2010

TO: Paijit Ostrowski, Regulatory Scientist, APP Pharmaceuticals, LLC 847-330-3952

THROUGH : Khushboo Sharma, Regulatory Project Manager, ONDQA

FROM: Khushboo Sharma, Regulatory Project Manager, ONDQA

SUBJECT: Memo of Telecon: Request for clarification on establishments information

APPLICATION/DRUG: NDA 201849

**Memo of Telecon:

The following clarifications were requested in a telephone conversation from Khushboo Sharma, RPM, ONDQA, to Paijit Ostrowski, Regulatory Scientist, APP Pharmaceuticals, LLC regarding establishment information submitted to the original NDA on FDA Form 356h Attachment:

1. Confirm the address of APP Pharmaceuticals, LLC (FEI 3005724920) as the address for this facility does not match with what we have in our EES system. Also, provide the corrected address as an amendment to the application.
2. Provide fax numbers for all the sites as an amendment to the application.

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

/s/

KHUSHBOO SHARMA
10/14/2010