CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201849Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	30 Apr 2015
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Review
NDA#	201-849
Applicant	APP Pharmaceuticals, a division of Fresnius Kabi USA, LLC
Date of Submission	8 Aug 2014
PDUFA Goal Date	8 May 2015
Proprietary Name / Established (USAN) names	No proprietary name Glucagon for injection
Dosage forms / Strength	lyophilized powder for injection (1 mg/vial)
Proposed Indication(s)	As a diagnostic aid for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract
Recommended:	Approval

Reference ID: 3749743

Cross Discipline Team Leader Review

1. Introduction

APP Pharmaceuticals/Fresnius Kabi LLC is submitting a New Drug Application (NDA) #201849 under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Glucagon for Injection. The listed drug is GlucaGen (Novo Nordisk; NDA 20918). This is a second cycle resubmission. The NDA received a Complete Response for the first cycle (see memo in DARRTS dated 24 Sep 2012). Note that while resubmissions are typically on a six-month clock, on 19 Dec 2014, a major amendment was received and the goal date was extended by 3 months to 8 May 2015.

This document contains the CDTL review of the NDA and serves as the Division decisional memo for the application.

2. Background

Glucagon is an endogenous hormone synthesized and secreted from the pancreatic alpha cells. Structurally, it is a 29-amino acid peptide, which acts on the liver to increase glucose production via glycogenolysis and gluconeogenesis, thereby effectively countering the effects of insulin. Two glucagon products—both produced from recombinant DNA expression—are currently approved in the United States for the treatment of severe hypoglycemia and also as a diagnostic aid to temporarily inhibit gastrointestinal motility. Novo Nordisk's GlucaGen was approved 22 Jun 1998 under NDA 20,918. Eli Lilly's Glucagon for Injection (no proprietary name) was approved under NDA 20,928 11 Sep 1998.

This review addresses a NDA for a synthetic glucagon for injection submitted by APP Pharmaceuticals a division of Fresnius Kabi USA, LLC (heretofore referred to as APP) under the 505(b)(2) pathway seeking approval only as a diagnostic aid for use (via intramuscular or intravenous injection) during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract, i.e. not the hypoglycemia indication.

APP's NDA relies on the Agency's findings of safety and effectiveness for the listed drug GlucaGen (Novo Nordisk; NDA 20918), a product produced through recombinant DNA technology. GlucaGen is approved for administration by subcutaneous (SC), IM or IV for the following indications: a) emergency use for treatment in severe hypoglycemia; b) as a diagnostic aid during radiologic examinations to temporarily inhibit gastrointestinal motility. To support their proposed 505(b)(2) regulatory pathway and reliance on FDA's previous determination of safety and effectiveness for the listed drug, the Applicant has provided scientific bridging data including CMC, nonclinical pharmacology/toxicology bridging studies and a relative bioavailability study.

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NDA 201,849 was originally submitted by APP on September 30, 2010, but was subject to a refusal-to-file action because it was not sufficiently complete to permit a substantive review. APP's original application [redacted] (b) (4) for use as a radiological diagnostic aid to temporarily inhibit the movement of the gastrointestinal tract. [redacted] (b) (4)

Additionally, there were pharmacology/ toxicology deficiencies contributing to the refuse to file (RFT) letter, specifically absence of non-clinical toxicology studies (28-day toxicity/TK study in rats and two geno-toxicity studies (Ames and chromosomal aberration assays).

The applicant resubmitted the NDA on 30 Nov 2011. The applicant addressed the Clinical refuse-to-file deficiency [redacted] (b) (4) and submitted the requested non-clinical studies. However, for the first cycle, the Applicant received a Complete Response Letter (CRL) (dated 12 Sept 2012) primarily due to Clinical Pharmacology's determination that the pivotal bioavailability study was not acceptable, as the glucose measurements in the study were not reliable.

The following deficiencies were listed in the CRL:

CLINICAL PHARMACOLOGY

We found significant deficiencies in the bioanalytical assay for glucose and therefore, the pivotal bioavailability study 200090101 titled "Bioequivalence of a Test Formulation of Glucagon for Injection, 1 mg (1 IU/mL) manufactured by Fresenius Kabi USA, LLC) compared to GlucaGen 1 mg (1 IU/mL) injection (manufactured by Novo Nordisk) Under Fasted Conditions" is not acceptable. Fresenius Kabi USA used a conventional diagnostic test procedure with single concentration calibration for the glucose measurements. This method is not compliant with 21 CFR 320.29(a) and not consistent with the methodology recommended by Guidance for Industry: Bioanalytical Method Validation (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf). Thus, the glucose measurements are not reliable. Of note, an information request during the course of the review revealed that the investigators did not retain plasma samples for glucose reanalysis. Therefore, a glucose re-assay of the samples using a validated method to potentially address this bioanalytical deficiency was not possible. In order to address these deficiencies, another bioequivalence study will need to be conducted.

FACILITY INSPECTIONS

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During a recent inspection of the Fresenius Kabi USA (3159 Staley Rd, Grand Island, New York) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

For a detailed summary of presubmission regulatory history, please see Dr. Cizza's Clinical review in DARRTS dated 1 May 2015.

The Applicant resubmitted the NDA on 8 Aug 2014, and a major amendment was received on 19 Dec 2014. The current memo pertains to this 'cycle 2' resubmission.

3. CMC/Device

This section summarizes CMC information from reviews conducted by reviewers from the Office of New Drug Quality Assessment (ONDQA) and from the Division of Medication Error and Prevention (DMEPA).

CMC:

Dr. Muthukumar Ramaswamy (ONDQA) reviewed the NDA for the second cycle (see review in Panorama dated 21 Jan 2015). From quality perspective, the NDA is recommended for approval. This approval recommendation is based on the current and past CMC reviews for this NDA application, a recommendation for approval from microbiology reviewer Dr. Metcalfe as well acceptable recommendation from Office of Compliance for the manufacturing facilities associated with this NDA.

The active ingredient /drug substance is glucagon, a synthetic 29 amino acid polypeptide (b) (4) [redacted]. Note that the amino acid sequences of the APP synthetic glucagon and the two U.S. approved recombinant glucagon products are identical to that of native human glucagon. The Applicant has referenced Type II DMF (b) (4) [redacted] for CMC information related to the drug substance, which is adequate to support the manufacturing of the drug product. Since the original NDA submission and subsequent resubmission (S007), the DMF holder has updated the drug substance manufacturing process, and provided updated specification for drug substance. The proposed update includes tightening of the assay specification range, limits for impurities in the drug substance and inclusion of a bioidentity test. The drug substance section of NDA resubmission (S009) contains updated specification for drug substance.

The drug product is a sterile, white lyophilized powder for injection, packaged as 1 mg per vial. The inactive ingredients (lactose NF and Water for Injection USP) (b) (4) [redacted] The product must be reconstituted with sterile water immediately prior to use. The NDA resubmission contains updated specification for the drug product which meets the current requirements for USP Glucagon for injection. The Applicant is using analytical procedures that are product specific or compendial methods. The Applicant has validated or qualified all non-compendial methods as appropriate.

No updates were provided for the Container Closure System, Stability data, or Environmental Assessment or claim of categorical exclusion.

Dr. Olen Stephens reviewed the NDA during the first cycle (see review in DARRTS dated 16 Aug 2012. Dr. Stephens concluded that there were no CMC deficiencies that would serve as the basis for not allowing approval of the NDA. However, because the Office of Compliance rendered a "withhold" recommendation (February 22, 2012), the CMC recommendation was nonetheless for a *Complete Response*. The withhold recommendation was based on deficiencies identified by an FDA field investigator during an inspection of the APP Pharmaceuticals facility as noted above.

To resolve this manufacturing deficiency, the drug product will be manufactured at Fresenius Kabi USA facility located at 2020 Ruby Street, Melrose Park, Illinois, i.e. the Applicant has removed, APP facility at Grand Island, NY from the list of facilities associated with this NDA. The Finished product will be tested for release and stability at either above Melrose Park, IL facility or at [redacted] (b) (4) On Aug. 25, 2014, the Office of Compliance issued an acceptable recommendation for all manufacturing and testing facilities associated with this NDA.

No post marketing requirements, commitments, or risk management steps are recommended.

<u>Device</u>:

DMEPA reviewed the revised container label [redacted] (b) (4) to determine if it is acceptable from a medication error perspective. The revisions consist of a new company trade dress, layout, and color changes (see Dr. Sarah Vee's reviews in DARRTS dated 3 Nov 2014 and 23 Apr 2015). The revised container label [redacted] (b) (4) are acceptable from a medication error perspective.

4. Nonclinical Pharmacology/Toxicology

The nonclinical data provided by the applicant consisted of a 4-week rat toxicology study and two *in vitro* gene toxicity studies (Ames and chromosomal aberration assay) comparing the drug product to the Listed Drug GlucaGen.

The pharmacology/ toxicology reviewers recommended this drug product for approval; see the first cycle review in DARRTS on 26 Jul 2012. Dr. Antonipillai noted that "overall drug exposure in the 28-day rat toxicity study was similar for the two drug products tested. She also notes that the total impurities tested in the 28-day toxicity study were "up to (b) (4)% with the APP drug product and up to (b) (4)% with the listed drug GlucaGen." The safety of the drug product and impurities was adequately qualified in the 4- week bridging toxicity study in rats with only "subtle toxicity" noted with the APP drug product but not with the listed drug.

The target organs of toxicity may be the heart in female rats (minimal to mild mineralization in

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2/8 rats at the high dose of 5 mg/kg/day, but not noted with the listed drug or controls) and the kidney in male rats (minimal to mild bilateral chronic progressive in 3/8 rats, but not noted with the listed drug or controls). Overall, Dr. Antonipillai concluded that the heart and kidney findings are mild and unlikely to have any clinical significance particularly if the product is used as intended (i.e., as a single-dose diagnostic).

This submission does not contain any new nonclinical pharmacology/toxicology data. Dr. Antonipillai again recommended approval of this NDA with no recommendations for postmarketing requirements or commitments. See her review in DARRTS dated 9 Dec 2014.

Dr. Antonipillai recommended some labeling changes to sections 8.1 (b) (4) of the proposed full Prescribing Information. Please see her review for details.

5. Clinical Pharmacology/Biopharmaceutics

Office of Clinical Pharmacology assessment

As noted, the pivotal study in this NDA is the 'repeated' relative bioavailability (BA) study of APP glucagon compared to the listed drug GlucaGen (GLUC-002-CP1). Dr. Jaya Vaidyanathan reviewed this study and has recommended approval of this NDA. Her review findings and conclusions are summarized below.

Also of note is that the current second cycle submission includes a relative BA study comparing the pharmacokinetics (PK)/pharmacodynamics (PD) of the APP glucagon product to the listed drug following subcutaneous (SC) administration while the relative BA study submitted with the original NDA was with the intramuscular (IM) route of administration.

Recall that the sponsor for the proposed glucagon for injection product is currently seeking approval for only the diagnostic indication (administration by IM and intravenous [IV] routes). (b) (4)

In study GLUC-002-CP1 the APP glucagon product met the PK BE criteria following 1 mg SC administration for the glucagon AUC_{inf} and C_{max} parameters (baseline uncorrected glucagon PK parameters) (See Table 1 taken from Dr. Vaidyanathan's review - Note that in Dr. Vaidyanathan's tables APP glucagon is called the synthetic glucagon and GlucaGen is called the reference glucagon).

Table 1: Statistical comparison of the PK parameters of synthetic glucagon and reference glucagon (baseline uncorrected) products following SC administration

Parameter	Test LS Means	Reference LS Means	Ratio	90% CI
Cmax (pg/mL)	3532.87	3308.96	106.77	94.05 – 121.20
AUC0-t (pg.h/mL)	3019.96	2462.14	122.66	111.38 – 135.07
AUCinf (pg.h/mL)	3071.92	2759.31	111.33	102.14 – 121.35

Dr. Vaidyanathan's review noted that while the AUC_{0-t} did not meet the regulatory criteria for BE, the percent extrapolation of the AUC_{inf} values were <10% for both the APP glucagon and the listed drug, therefore, the exposure from the two products is considered to be bioequivalent. Dr. Vaidyanathan explained further that for BE determination, typically Cmax and AUC_{inf} is used. However, the confidence in the AUC_{inf} parameter will depend on how close the estimation is to the AUC0-t and here it is <10%. The guidance recommends the reliability of AUC_{inf} as long as the extrapolation is < 20%.

The glucose (PD; baseline corrected glucose) parameters also met the BE criteria (Table 2 taken from Dr. Vaidyanathan's review).

Table 2: Statistical comparison of baseline corrected glucose parameters for the synthetic glucagon and reference glucagon products following SC administration

Parameter	Least-Square Means		Ratio	90% Confidence Intervals	
	Test	Reference		Lower CI	Upper CI
Cmax	941.47	991.65	94.94	86.22	104.54
AUC0-2	921.54	927.54	99.35	85.64	115.26
AUC0-4	979.16	958.87	102.12	88.04	118.45

OSI inspection was conducted for this pivotal bioavailability study. (See Dr. Xikui Chen's memo in DARRTS dated 5 Jan 2015). The inspection found that the bioanalytical site [redacted] (b) (4) failed to accurately calculate the concentrations of the analyte glucose for calibration standards, quality control samples and study plasma samples for the assays in this study. Specifically, [redacted] (b) (4) failed to take into account the specific gravity of the glucose solution for calculation of primary stock, sub-stock, calibration standard and quality control sample concentrations. It was suggested by OSI that [redacted] (b) (4) measure the specific gravity of the glucose solution and re-regress data using updated concentrations. [redacted] (b) (4) submitted an amended clinical study report on 19 Dec 2014. The Agency coded the submission as a major amendment and resulted in extension of the PDUFA goal date. It is important to note that the data in Dr. Vaidyanathan's Table 2 show the original data. However, the amended data are very similar to the original and do not change the overall conclusions. The amended data are available in Table 8 in Dr. Vaidyanathan's review.

As noted in Table 2 above, the LSM means between baseline-corrected AUC0-2 and AUC0-4 for both formulations are less than 1% different. The individual profiles indicate that most baseline-corrected concentrations were zero after Hour 2. According to Dr. Vaidyanathan, data from literature also indicate that the glucose levels reach baseline values within 2 hours post-dose.

Further, the time to peak glucagon and glucose were comparable between APP glucagon and the listed drug. The median T_{max} for glucagon in the first and second treatment periods for the APP glucagon was 12.6 min and 10.2 min, respectively, while the median T_{max} for the listed drug was 15 min in both first and second replicate treatment periods. The median time for the maximum blood glucose for the APP glucagon was 50 min in the two replicate treatment periods, while it was 40 min and 50 min, respectively in the first and second replicate treatment period for the listed drug.

The Clinical Pharmacology reviewers concluded similarity in the absorption characteristics (rate and extent) from the SC injection site between the APP glucagon and listed drug as well as similarity in the glucose response characteristics indicating that the *in vivo* PD activity of glucagon is preserved with the APP glucagon product.

Additional supportive information for establishment of bioequivalence comes from the PK data from the previous submission containing the BE study following IM administration. As discussed in the first cycle Clinical Pharmacology review (dated 27 Aug 2012 in DARRTS), the glucagon PK parameters met BE criteria following IM administration (based on AUC and C_{max} parameters) (Table 3 from Dr. Vaidyanathan's review).

Table 3: Statistical comparison of the PK parameters of baseline uncorrected synthetic glucagon and reference glucagon products following IM administration

Parameter	Test A (N=50)	Reference B (N=50)	Ratio	CI*	Intra-Subject %CV
AUC0-t (pg·hr/mL)	2829.16	2959.26	0.9560	0.9078 - 1.0069	21.9512
AUC0-inf (pg·hr/mL)	2947.78	3074.50	0.9588	0.9094 - 1.0108	21.5108
Cmax (pg/ml)	3391.01	3817.62	0.8883	0.8198 - 0.9625	28.5482

Dr. Vaidyanathan notes that although the PD data (plasma glucose) from the IM study did not clearly establish bioequivalence, it is expected that the PD of the synthetic glucagon *via* the IM route will be similar to the listed drug because of SC PK and PD bioequivalence and because of the known dose-response relationship of glucagon which indicates that glucagon response is saturated at very low doses of glucagon (0.25 mg). The 1 mg dose is expected to result in maximal clinical response.

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Immunogenicity

We requested immunogenicity review from the Office of Biotechnology Products (OBP)/ Division of Therapeutic Proteins. See the consult review dated 16 Dec 2014 in Panorma, completed by Dr. Steven Bowen and Dr. Susan Kirschner. Note that no immunogenicity assessments were done during the development of this product. OBP recommended that due to the weak immunogenicity of purified glucagon demonstrated in previously conducted studies with other glucagon polypeptides, no post-marketing requirement was needed to assess glucagon immunogenicity at this time.

Particularly of note, the Sponsor of the listed drug (GlucaGen) conducted a parallel, randomized study to assess immunogenicity of both recombinant and animal-source glucagon in 75 subjects. The study involved 3 intramuscular injections of recombinant (N=50) or animal-source (N=25) glucagon 3 weeks apart. Anti-glucagon antibody levels at baseline and at 6-weeks following the final injection were below the limit of detection for both treatment groups.

Please see the OBP consult review for further details.

6. Clinical Microbiology

This submission does not contain any new clinical microbiology data. On 15 Aug 2012, Microbiology reviewer, Dr. Metcalfe, recommended approval of this NDA.

7. Clinical/Statistical- Efficacy

This application contains a single, clinical pharmacology (relative bioavailability or bioequivalence) study and no other clinical trials evaluating safety or efficacy of APP's synthetic glucagon product. Please refer to Section 5 of this review for a discussion of the bioequivalence study design and the pharmacokinetic and pharmacodynamic findings.

8. Safety

As with effectiveness, the applicant is relying on the Agency's findings of safety for the listed drug GlucaGen.

As noted in Dr. Calis's CDTL memo from the first cycle, the relative BA study with the IM route of administration involved 32 healthy volunteers and was largely unremarkable from a safety perspective and consistent with the known safety profile of glucagon. There were no clinically relevant changes in vital signs or laboratory parameters.

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The most frequently reported adverse events for the APP glucagon (Table 3) were nausea (5 participants) and vomiting (2 participants); the most frequently reported adverse events for the listed product GlucaGen were also nausea (4 participants) and vomiting (2 participants). Injection-site reactions were not reported in the study, in contrast to the SC study (see below).

Table 3 – Adverse Reactions in the IM Relative Bioavailability Study for APP Glucagon and the Listed Drug Glucagen

	APP Glucagon n (%)	GlucaGen n (%)
Gastrointestinal Disorders		
Nausea	5 (17.24%)	4 (12.90%)
Vomiting	2 (6.90%)	2 (6.45%)
General Disorders and Administration Site		
Weakness	1 (3.45%)	0 (0.00%)
Hyperhidrosis	1 (3.45%)	0 (0.00%)
Investigations		
Heart rate decreased	0 (0.00%)	1 (3.23%)
Tryglycerides increased	0 (0.00%)	1 (3.23%)
Nervous System Disorders		
Dizziness	1 (3.45%)	1 (3.23%)
Headache	0 (0.00%)	1 (3.23%)
Total	**9 (31.03%)**	**8 (25.81%)**

N% = (Number of subjects reporting AE/number of subjects dosed with respective study drug) × 100 Total N%= (Number of subjects that reported at least one AE/number of subjects dosed with study drug) × 100

The safety findings from the SC pivotal relative BA study were similarly unremarkable. Please see Dr. Cizza's Clinical review for details.

A comparison of adverse reactions from the two relative BA studies is shown in Table 4. (Note that these are two separate studies and cross-study comparison is not appropriate). In general, because in the current NDA the Applicant is seeking approval for the IM route of administration it is recommended to show the adverse reaction data from the IM study rather than the SC study. If the Applicant were to submit an sNDA for the SC route of administration the adverse reaction data from the SC study should be added to the label at that time. As stated above, the major difference between the two routes of administration is that injection site reactions were observed at a high frequency with the SC route of administration but were not observed with the IM route of administration. These are not labeled adverse reactions in the GlucaGen label and are not recommended to be included in the APP glucagon label because they were not observed with the intended route of administration, i.e. the IM route. Additionally, decreased blood pressure and headache (at lower frequencies) were observed with the SC route of administration. Decreased blood pressure is labeled in section 6 in the GlucaGen label and because of the route of administration is not specified it is acceptable to keep this in the APP glucagon label. Headache is not in the GlucaGen label and is not recommended to be included in the APP glucagon label for the same reasoning that applies to injection site reactions.

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Table 4 – Adverse Reactions Observed in the SC and IM Relative Bioavailability Studies

APP Glucagon for Injection, 1 mg administered subcutaneously	% of Patients (N=31)	**APP Glucagon for Injection, 1 mg administered IM**	% of Patients (N=29)
Injection site swelling	58%	Nausea	17.24%
Injection site redness	55%	Vomiting	6.90%
Vomiting	36%	Weakness	3.45%
Nausea	32%	Hyperhidrosis	3.45%
Asthenia	23%	Dizziness	3.45%
Decreased blood pressure	23%		
Headache	13%		

9. Advisory Committee Meeting

No advisory committee meeting was convened for this sNDA.

10. Pediatrics

This submission does not trigger new pediatric studies under the Pediatric Research and Equity Act (PREA) because the application does not provide for a new active ingredient, new dosage form, new route of administration, new indication, or new dosing regimen.

11. Other Relevant Regulatory Issues

None identified

12. Labeling

Labeling input was provided by Dr. Eric Brodsky from SEALD. Dr. Brodsky concurs with the current and 'final' version of labeling as submitted by the Applicant at the time of this review. As per best labeling practice for a 505(b)(2) NDA, original data for APP glucagon for injection is presented where appropriate/available, while the remainder of the label should is populated with data from the listed drug GlucaGen, with the exception that labeling for this product shows information relevant for the indication of diagnostic use for radiologic procedures, i.e. not the emergency treatment of hypoglycemia indication, and for the IM and IV routes of administration, and is written as to not present data that would give an implied indication for such use. Further, the label has been 'updated' to reflect current labeling rules, and in many cases does not follow the exact format of the listed drug.

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Specific points of interest:

For section 1 the following statement is recommended:
Limitations of Use:
Glucagon for Injection is not indicated for the emergency treatment of hypoglycemia (1)

For section 2, recommended changes include simplifying anatomic location to 'small bowel' from [redacted] (b) (4) Other sections are simplified as well for readability.

Adverse reaction data in the GlucaGen label is limited and does not clearly distinguish between clinical study data and spontaneously reported postmarketing data. In section 6 of the full Prescribing Information for APP glucagon, a table showing frequencies of adverse reactions obtained from the IM relative BA study submitted with the original NDA is recommended. [redacted] (b) (4)

In section 8, the pregnancy category is retained because the Applicant is not proposing an updated section 8 consistent with the Pregnancy and Lactation Labeling Rule (PLLR) which goes into effect 30 Jun 2015.

The following comment was provided by DMEPA during the original NDA review: "We wonder if the statement "Glucagon as Hydrochloride 1 mg [redacted] (b) (4)" is necessary. We suggest deleting the statement if it is not needed. If it is needed, we suggest relocating to the side panel of the label, and revise to state "Glucagon as Hydrochloride 1 mg" [redacted] (b) (4) The Applicant has agreed to remove [redacted] (b) (4) information from the label.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant has provided an adequate scientific bridge to the listed drug GlucaGen such that reliance on FDA's previous determination of safety and effectiveness for approval of the Applicant's glucagon for injection is justified.

This scientific bridge is based in part on CMC and nonclinical pharmacology/toxicology studies, e.g. 4-week rat toxicology study and two *in vitro* gene toxicity studies (Ames and

chromosomal aberration assay). The 4-week rat toxicology study is adequate in duration because APP glucagon for injection is intended for single use. The pivotal relative bioavailability study demonstrated that bioequivalance criteria were met for both pharmacokinetic absorption characteristics (rate and extent) from the SC injection site between the APP glucagon and listed drug as well as similarity in the glucose response characteristics indicating that the *in vivo* PD activity of glucagon is preserved with the APP glucagon product. The PK/PD bridging supports the approval of the IM and IV route of administration given that the relative BA study *via* the IM route showed PK BE between APP glucagon and the listed drug, and because of the known PK/PD relationship for glucagon from the literature showing similar PD response among the SC, IM, and IV routes of administration for the same dose.

Finally, there were no unexpected safety findings with the safety data collected from either of the relative BA studies.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

None

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/s/

LISA B YANOFF
05/07/2015

JEAN-MARC P GUETTIER
05/08/2015

I concur with Dr. Yanoff and recommend approval. Dr. Yanoff's review serves as the Division's summary basis for approval for this application. In brief, Fresenius Kabi LLC submitted a new drug application pursuant to section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FD&C Act) for glucagon for injection for use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal (GI) tract. The applicant relies, in part, on FDA's finding of safety and effectiveness for the listed drug GlucGen [glucagon (rDNA origin) for injection; NDA# 020918] to support approval of glucagon for injection. The applicant has submitted toxicology and clinical pharmacology studies, summarized in Dr. Yanoff's review, that provide the scientific rationale supporting that reliance on FDA's previous finding of safety and effectiveness of GlucaGen is justified. These data, together with product-specific data, establish the safety and effectiveness of glucagon for injection for its proposed condition of use.