CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210134Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110674

MEETING MINUTES

Locemia Solutions U.L.C.
Attention: Claude A. Piché, D.V.M., M.Sc.
President and C.E.O.
400 Canton Walk
Roswell, Georgia 30075

Dear Dr. Piché:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG504-1 (glucagon) intranasal powder.

We also refer to the meeting between representatives of your firm and the FDA on May 7, 2015. The purpose of the meeting was to obtain Agency feedback on the proposed nonclinical, clinical, and CMC package to be submitted in support of a 505(b)(2) NDA for AMG504-1.

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

If you have any questions, call Marisa Petruccelli, Regulatory Project Manager at (240) 402-6147.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
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:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 7, 2015, 9:00 AM – 10:00 AM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 110674
Product Name:	AMG504-1 (glucagon) intranasal powder
Indication:	Treatment of severe hypoglycemia (b) (4) .
Sponsor/Applicant Name:	Locemia Solutions
Meeting Chair:	Jean-Marc Guettier, M.D.
Meeting Recorder:	Marisa Petruccelli

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Division Director
Stephanie Leuenroth-Quinn, PhD, Acting Nonclinical Team Leader
Parvaneh Espandiari, PhD, Nonclinical Reviewer
William Chong, M.D., Clinical Team Leader
Suchitra Balakrishnan, M.D., PhD, Clinical Reviewer
Ondina Lungu, M.D., Clinical Reviewer
Julie Van der Waag, MPH, Chief, Project Management Staff
Marisa Petruccelli, Project Manager

Office of Pharmaceutical Quality

Suong Tran, PhD, Drug Product Quality Lead, ONDP/DNDPII
Joseph Leginus, PhD, API Quality Reviewer, ONDP/DNDAPI
Mohanraj Manangeeswaran, PhD, Reviewer, Laboratory of Immunology

Office of Biostatistics

Gregory Levin, PhD, Biometrics Team Leader
Cynthia Liu, MA, Biometrics Reviewer

Office of Clinical Pharmacology

Manoj Khurana, PhD, Acting Clinical Pharmacology Team Leader
Sang Chung, PhD, Clinical Pharmacology Reviewer

Center for Devices and Radiologic Health

Jason To, Combination Products Reviewer
Alan Stevens, CC, Infusion Pump Team Leader
Richard Chapman, BA, MS, Chief, General Hospital Devices Branch

Office of Surveillance and Epidemiology

Mona Patel, Pharm.D, Senior Drug Risk Analyst, Division of Risk Management
Yelena Maslov, Pharm.D, Team Leader, Division of Medical Error Prevention and Analysis
Sarah Vee, Pharm.D, Safety Evaluator, Division of Medical Error Prevention and Analysis

Office of Scientific Investigations

Cynthia Kleppinger, M.D., Medical Officer

Office of Combination Products

Patricia Love, M.D., MBA, Deputy Director
Bindi Nikhar, M.D., Associate Director

SPONSOR ATTENDEES
Claude A. Piché, DVM, MSc; President & CEO, Locemia Solutions
Ronith Afar, Ph.D.; Director, Regulatory Affairs, Locemia Solutions
Patricia Stotland, BSc; Director, Regulatory Affairs, Locemia Solutions
Myriam Triest, Ph.D.; Director, Product Development, Locemia Solutions
Hélène Dulude, B.Pharm, Ph.D.; Director, Clinical Development Research, Locemia Solutions
(b) (4) .
(Regulatory Consultant)
(b) (4) (Regulatory Consultant)
(b) (4) (Toxicology Consultant)
(b) (4)
(Clinical Consultant)

[redacted] (b) (4)
(Statistical Consultant)
[redacted] (b) (4) (Clinical and Regulatory Consultant)
[redacted] (b) (4) (Human Factors Consultant)

1.0 BACKGROUND

The purpose of this meeting is for the sponsor to obtain Agency feedback on the proposed nonclinical, clinical, and CMC package to be submitted in support of a 505(b)(2) NDA for AMG504-1 glucagon nasal powder. This drug product is indicated for the treatment of severe hypoglycemia, which may occur in patients with diabetes mellitus treated with insulin. The proposed drug product is a drug/device combination product that consists of a [redacted] (b) (4) device [redacted] (b) (4) that is intended to deliver a single dose of 3 mg glucagon to the nasal passage upon activation.

Design details for the [redacted] (b) (4) device are the subject of a device master file. The sponsor intends to reference the master file and provide technical information on the device in Module 3.2.P.7 of the 505(b)(2) NDA; including the biocompatibility testing and physiochemical testing in accordance with the requirements of ISO 10993-1 and USP <661>, respectively, as discussed in the End-of-Phase 2 meeting of April 15, 2013.

Regulatory History: The sponsor submitted a Pre- Investigational New Drug (PIND) meeting request on November 26, 2010, which we denied. The sponsor subsequently submitted a new IND on April 5, 2012, which we allowed to proceed after the 30 day safety period. The sponsor submitted the first End of Phase 2 (EOP2) meeting request on July 6, 2012, which we denied and asked the sponsor to provide the full clinical study report (CSR) for the study entitled "A Single Site, Randomized, Three-way, crossover Phase 2 Study To Investigate The Safety And Efficacy Of 2 Dose Levels Of A Novel Glucagon Formulation Compared To Commercially Available Glucagon In Type 1 Diabetic Patients Following Insulin-Induced Hypoglycemia" for our review. The sponsor submitted the full CSR on December 14, 2012.

The sponsor submitted a second EOP 2 meeting request on January 24, 2013, which we granted. The face to face meeting took place on April 15, 2013.

On February 12, 2015, we received a pre-NDA Type B meeting request from Locemia Solutions for IND 110674 AMG504-1, a novel, non-injectable glucagon for treatment of severe hypoglycemia. On February 25, 2015, we granted a pre-NDA Type B meeting for May 7, 2015.

FDA sent Preliminary Comments to Locemia Solutions on May 1, 2015.

2. DISCUSSION

2.1 Regulatory

Question 1: Recognizing the serious limitations of the current glucagon delivery systems for intended users, does the Agency agree that AMG504-1 fulfills an unmet medical need for a

glucagon delivery system that can be used effectively in an emergency situation by caregivers of persons using insulin, and that a request for priority review designation is appropriate?

FDA Response to Question 1:
If you choose to make a request for priority review, a decision regarding standard or priority review will be made at the time of filing.

Meeting Discussion: No further discussion.

Question 2: Does the Agency agree that, based on the inclusion of new clinical investigations, the approval of the 505(b)(2) NDA for AMG504-1 will meet the requirements for 3.5 year exclusivity?

FDA Response to Question 2:
Under 21 CFR 314. 108(b)(4), the inclusion of new clinical investigations (other than bioavailability studies) conducted on behalf of the applicant, essential to the approval of the application, and not previously relied on by the FDA for efficacy would make this application eligible for a three year period of exclusivity.

Under the 2002 Best Pharmaceuticals for Children Act (BPCA), an additional six months of exclusivity may be granted to sponsors who submit a Proposed Pediatric Study Request (PPSR) and are issued a Written Request. If it is determined that the pediatric studies submitted are in accordance with the terms of the Written Request and the six-month period of exclusivity is granted, this period is added to any existing exclusivity on all applications held by the sponsor for that active moiety. This six-month period of exclusivity will only attach if nine or more months remain on current exclusivity at the time of pediatric exclusivity determination.

Meeting Discussion: No further discussion.

Question 3: Does the Agency agree with the proposed risk management plan and that a REMS is not required for AMG504-1?

FDA Response to Question 3:
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of AMG504-1 outweigh the risks, and if it is necessary, what the required REMS elements will be. The need for a REMS will be determined during the review of the application.

The NDA submission does not need to include a REMS proposal in order to be filed.

Meeting Discussion: No further discussion.

Question 4: Does the Agency agree that GlucaGen® (glucagon [rDNA origin] for injection) labeling in PLR format from Novo Nordisk A/S (NDA 020918), supplemented with information from other labeling sources, is appropriate as the basis for developing the AMG504-1 labeling?

FDA Response to Question 4:
Using the PLR format labeling for GlucaGen as a template for your product labeling is acceptable. However, it is premature to discuss labeling details at this time. We note that your labeling proposal in the pre-NDA meeting package includes a series of changes to the GlucaGen labeling and will provide comment on the proposed label during the review.

Meeting Discussion: No further discussion.

Question 5: Does the Agency agree with the proposed inclusion of data from pivotal clinical studies (b) (4) of AMG504-1 in the labeling?

FDA Response to Question 5:
It is premature to discuss any labeling details at this time. (b) (4)

Meeting Discussion: No further discussion.

Question 6: Does the Agency agree that, in accordance with the agreed SPA, demonstration of 10% non-inferiority compared to injected glucagon in achieving the primary endpoint (study AMG106) is sufficient to support the label indication?

FDA Response to Question 6:
The 10% non-inferiority margin is consistent with the agreed SPA. Whether the totality of the data support approval will be a decision made during the review.

Meeting Discussion: No further discussion.

Question 7: Does the Agency agree with the proposed organization of the eCTD 505(b)(2) NDA?

FDA Response to Question 7:

A. General eCTD Comments

From a technical standpoint (not content related) yes, the proposed format for the planned NDAs are acceptable. However, please see additional comments below

1. Study Tagging Files (STFs) are not required for m2 or m3. STFs are only required for m4 and m5.

2. Providing a single 2.3.s, 2.3.p, 3.2.s, and 3.2.p sections with attribute of "ALL" and differentiating documents by leaf title, is acceptable. The preferred method of

differentiating documents is with clear and concise leaf titles that indicate the file's true content (e.g. general information-Glucagon, general information- (b) (4) **).**

3. Do not create additional nodes in the eCTD structure beyond what is in the eCTD Specifications (e.g. m2.7.3, m2.7.4, etc.,). They could be a single pdf file but with proper bookmarks, table of contents, and hyperlinks.

4. Make sure that all documents have proper page orientation. The proposed TOC had to be rotated, accordingly.

5. Providing Table of Contents in m5.1 is not necessary in the eCTD structure.

6. The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be hyperlinked to the referenced studies in m5.

7. Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5, with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and m5.3.6, if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (crfs).

Case report forms need to be referenced under the appropriate Study Tagging File (STF) to which they belong, organized by site as per the specifications and tagged as "case report form". Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf

B. eCTD Location of device constituent part information

As noted above, please do not change the name of the headings to accommodate the device information. Also, do not use node extensions to create new elements. When including and referencing device information we recommend the following:

1. **We request an "Information to Reviewers" or "Reviewers Guide" document in Module 1.2 Cover letters to identify the location of the device information. This document would be separate from the cover letter and referenced after the cover letter. It would provide a high level overview (with reference links) of the submission's content and list where the information is located in the eCTD. For example, it would identify where drug, device, and combination product information is located.**

2. **Use Module 1.4.4 to cross reference another company's device application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 Letter of authorization, 1.4.2 Statement**

of right of reference, 1.4.3 List of authorized persons to incorporate by reference). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.

3. **All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21 CFR Part 4 and the applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3. For more information on Part 4 see FDA Additional Comments section.**

    a. **The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.**

    b. **Suggestions on the types of documents to submit for review of required sections of 21 CFR Part 820 (based upon the combination product 21 CFR Part 4 GMP operating system at the facility) can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003 and accessible at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm.**

4. **You may reference container closure (nasal device constituent) files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.**

    a. **In 3.2.P.7 you could include a leaf titled something similar to the following, "Table of Contents for Drug-Device Descriptor/Name. This leaf/document could provide reference links to the other files in module 3.2.P.7. Obtaining concurrence from the Review Division on the proposed outline is recommended.**

    Meeting Discussion: Locemia Solutions proposed to provide a detailed TOC for the device related information. FDA recommended that the information be provided along with the applicant's future Type C meeting request to address other items related to the current meeting discussions.

    b. **The leaf titles should be clear, concise, and indicative of the document's content.**

Question 8: Does the Agency agree that the sponsor's proposal to submit analysis datasets (in ADaM format) only for the results included in the ISS and ISE and not the individual studies?

FDA Response to Question 8:
The analysis datasets in ADaM format for ISE and ISS should have a study identifier so that the data for each study can be extracted directly without data manipulation, and can be used to reproduce the results shown in your clinical study reports. We request that raw datasets be submitted for the PK/PD studies as well.

Meeting Discussion: The sponsor confirmed that they will submit raw data for individual studies in SDTM format and that individual studies will be adequately identified in the ADaM analysis dataset (ISS and ISE). Raw datasets will be submitted for the PK/PD studies. The Agency agreed that this approach is reasonable.

2.2 Chemistry, Manufacturing and Controls

Question 9: Does the Agency agree that the proposed drug substance specification and analytical procedures are adequate to demonstrate the quality of the synthetic glucagon drug substance?

FDA Response to Question 9:
We agree that the monograph for glucagon is able to serve as the basis for release specifications for your drug substance. However, additional testing methods and acceptance criteria should be included that are specific to your drug substance manufactured by different processes and suppliers (e.g., identification and levels of impurities and residual solvents). The adequacy of the proposed test methods, their validation, and acceptance criteria will be determined at the time of NDA review.

We remind you:

a. To provide a tabular summary identifying the drug substance batches (batch numbers and manufacturers) used in the manufacture of AMG404-1 drug product. Also include the corresponding drug product batches detailing their use in development, stability, and Phase 1, 2 and/or 3 clinical studies.

b. You will also be required to demonstrate comparability between the drug substances from the different sources of glucagon and the resulting drug products. At the time of NDA submission, include a thorough comparison of impurities/degradants in batches of drug product manufactured with the drug substances from different sources. The analytical quality testing should include a side-by-side comparison of the two products including batch release data, stability data (long-term, accelerated, and stress), and degradant characterization data (i.e., degradation trends, identification of degradants) for product batches. Nonclinical studies may be required to qualify any difference in the impurity/degradant profile. A conclusion regarding the comparability of the same drug substance from different suppliers will be made based upon data submitted in the NDA.

Meeting Discussion:

The sponsor will submit a Type C "written response" request with the comparability data (that FDA requested in item b. above) for FDA's additional input.

Question 10: Does the Agency agree that the proposed in-process, release and shelf-life specifications and analytical procedures are adequate to demonstrate the quality of AMG504-1 Glucagon Nasal Powder?

FDA Response to Question 10:
We do not agree with your proposed specifications as adequate. We have the following comments:

a. At the time of NDA submission, optimize and justify in-process specifications for (b) (4) which currently have wide ranges. As appropriate, include a specification for (b) (4)

b. Propose acceptance criteria for the following finished product attributes:
i. Assay of glucagon content (% LC)
ii. Uniformity of the dosage units per USP <905>
iii. Uniformity of the delivered dose (Include Tier 1 (n=10) and 2 (n=30) acceptance criteria for the individual and mean of all individual dose results, (expressed as % of LC, not based on shot weight)
iv. Shot weight (pump delivery)
v. Plume geometry
vi. Foreign particulates
vii. Bioidentity test

c. In general, an overfill is used to compensate for the amount retained (holdup volume) in the device. At the time of NDA submission propose appropriate justification for the overfills used in the container.

Meeting Discussion: The sponsor will submit a Type C "written response" request with the data that FDA requested above for FDA's additional input.

Question 11: Does the Agency agree with the sponsor's proposal to use a semi-quantitative method to measure the particle size of the AMG504-1 glucagon nasal powder?

FDA Response to Question 11:
In the absence of a reliable quantitative method for use, the use of a semi-quantitative method is reasonable approach to control quality. At the time of NDA submission, describe your efforts to measure the PSD of emitted dose (Laser diffraction in air) and also document your efforts to develop alternate methods for reaching the same objective.

Meeting Discussion: No further discussion.

Question 12: Does the Agency agree that the information to be included for the (b) (4) device is adequate to support a 505(b)(2) NDA?

FDA Response to Question 12:
No, we do not agree. Based on the information provided within the meeting package for the device constituent of your combination product, the data you propose to include to support the (b) (4) device appears to be limited and is therefore not sufficient to demonstrate the safety and efficacy of your device. The information that you have provided within your meeting package is not clear, comprehensive, or adequately described. Therefore, the FDA cannot conduct a substantive review and provide a clear decision or determination regarding the acceptability of the information that you propose to include for the (b) (4) device in support of a 505(b)(2) NDA. As it relates to your device, please be advised that you are required to provide complete information regarding the design control activities that you have conducted for your device in order for the FDA to complete a full review of device materials within your future submission. The following comments below contain recommendations regarding the types of information relating to your device that the FDA expects to see contained within your future submission. Please note that additional information and/or performance testing may be required in order to demonstrate the safe and effective use of your device based on the review of your future submitted documentation.

General Device Design Descriptions

a. A complete and detailed description of your device design and delivery system, including any features and functionalities unique to your device.

b. Detailed descriptions of the principles of operation of your device, from beginning to end of the activation process, in which you explain the mechanical drug delivery mechanisms of your device in order for it to achieve its intended use.

c. Engineering drawings and detailed descriptions of individual device components. You should identify any single-fault performance critical components, and explain how your device design and implemented safety mitigations will ensure that your device will be reasonably reliable and robust.

d. Proposed labeling and Instructions for Use.

e. Descriptions of the proposed packaging for the device.

Device Risk Analysis

It is recommended that you conduct a comprehensive risk analysis for your device and provide this information within your future submission. This analysis will need to characterize and assess the potential risks posed to the user during correct normal use, probable misuse, and in situations where there is a potential device system failure that prevents the device from achieving its intended use. You will need to clearly describe the

potential hazards that are apparent to your device, describe the safety mitigations you have implemented to address the identified hazards, explain why these mitigations are acceptable, and provide evidence that demonstrates the effectiveness of those mitigations. Further, you will need to provide scientific rationale and clinical justification regarding the acceptability of any residual risks posed within the final finished device system. Also, please ensure that you provide detailed descriptions of the mitigations that you have implemented in order to address the risks associated with false activation, partial activation, and/or unintentional lock-out of your device.

Device Performance Testing – Verification and Validation Activities

You will need to conduct performance testing for your device in order to adequately demonstrate that your delivery device is reliable and can accurately administer its intended dose requirement consistently. You will need to assess the functionalities of your device and show that your device maintains its integrity and functions as intended throughout its entire use life cycle. Therefore, you should provide the following within your future submission:

a. A complete and detailed device design requirements and specifications document, which includes a comprehensive outline of design control inputs as well as clear descriptions of the characteristics of the device. Ensure that you clearly describe the acceptability of your design control inputs within the context of the intended use of your combination product.

b. Comprehensive design output information, which includes complete test reports and other applicable test activities used to verify and validate your device design requirements and specifications within the context of the intended use of your combination product. Ensure that you utilize test methods and procedures that simulate the in-field use of your product in order to verify that your final finished device with actual drug product meets your design requirements and specifications and provide detailed rationale for your test acceptance criteria. This includes providing explanations for any deviations from initially outlined protocols and procedures, as well as providing valid justifications for any test results not being able to pass its acceptance criteria, if applicable. Furthermore, you should utilize a sufficient number of device test samples that will be statistically relevant for your performance testing.

Your verification and validation activities for the device constituent part of your combination product should include, but are not limited to, the following: dose accuracy, force required to initiate drug delivery (actuation force, device mechanical reliability and robustness (i.e. forces required to attach and detach device components are reasonable to prevent unintended mechanical device failure or separation of device components), container closure integrity (i.e. integrity is not compromised and there is reasonable resistance against leakages or ingress of unwanted particles or liquid), actuation and presence of any implemented device safety features, sterility of applicable device components (if applicable), and biocompatibility of patient-contacting and drug-contacting device components. It is important to note that you should consider conducting additional

performance testing as it relates specifically to the unique design and the intended use of your device.

In addition to these post-manufacturing verification and validation activities, you should also provide functional performance test data for your device, in which you utilize a sufficient number of device test samples that have been pre-conditioned and subjected to extreme thermal, physical, and chemical conditions in order to demonstrate that your device is reliable and robust when exposed to worst case use environments. Specifically, you will need to verify and validate that your device will be able to meet its essential safety and performance requirements after pre-conditioning activities, including, but not limited to, the following items: physical forces (i.e. drops and vibration), environmental conditions (i.e. temperature and humidity), shipping and transportation, storage environments, sterilization, and aging commensurate with your proposed shelf-life. This is required to demonstrate that your device is capable of achieving its intended use throughout its use life cycle should it be subjected to unexpected worst case conditions in the field.

Please note that additional information and/or performance testing may be required in order to demonstrate the safe and effective use of your device based on the review of your future submitted documentation.

Please confirm that the delivery device used in your phase 3 development is the same as the to-be-marketed product. If this is not the case, please propose a bridging strategy.

Meeting Discussion:

Locemia Solutions indicated that they did not design the device and do not have development details. Also, the device was modified after completion of the clinical trial. The firm characterized the changes as minor:

1) [redacted (b) (4)] *With the modification* [redacted (b) (4)] *the device has been fired and reduces the risk of a patient carrying an empty device as a rescue medication;*

2) To provide a clear indication that the device has been correctly fired, a [redacted (b) (4)] *colored band was added to the end of the plunger so that instructions could include a visual cue (i.e., press the plunger until the* [redacted (b) (4)] *colored band disappears into the bottom of the device).*

FDA did not comment on the acceptability of these changes. However, as the NDA holder, Locemia is ultimately responsible for the combination product.

Post-meeting Comment: The NDA should include details on all device modifications, the purpose for the change, a risk analysis of the change, and data to demonstrate that the change resolved design concerns and did not introduce new concerns. You may cross reference the

device developer's master file (with the device developer's letter of authorization to cross reference the data).

Question 13: Does the Agency agree that these data presented together with the biocompatibility testing of critical components of the device according to ISO 10993-1 and extractables testing according to USP<661> are sufficient to support the AMG504-1 505(b)(2) NDA and no further leachables testing is required?

FDA Response to Question 13:
After a review of your biocompatibility data, the Agency agrees with your proposed testing strategy for the critical components of your device using ISO 10993-5 (cytotoxicity) and ISO 10993-10 (skin sensitization and intracutaneous reactivity). In regards to extractables and leachables from your device, we recommend that you perform an exhaustive extraction at 50°C with a polar and nonpolar solvent as per ISO 10993-12 and provide a risk assessment for each extractable and leachable compound for the worst case patient considerations (e.g., most vulnerable patient population with considerations of multiple patient exposures).

Meeting Discussion: No further discussion.

Question 14: Does the Agency agree that the minor modifications implemented during development (i.e., composition, manufacturing process and controls) do not impact the quality of the final drug product proposed for commercial manufacturing upon approval of NDA?

FDA Response to Question 14:
Considering that you do not have any data from commercial scale batches, it is premature to provide any agreement to your question. Your question will be an issue to be evaluated during our review of the complete NDA.

At the time of NDA submission, provide sufficient powder characterization data for the proposed drug product. Include data on bulk density, size, shape, and charge of the particles present in nasal powder, and reproducibility of the device performance under various actuation speeds.

Meeting Discussion: The sponsor will submit the requested data in the NDA.

Question 15: Does the Agency agree that the stability data package is sufficient to support approval of the 505(b)(2) NDA?

FDA Response to Question 15:
Yes, we agree with the proposed stability package. In addition, we remind you to provide a minimum of three-month real-time and accelerated stability data from a minimum of three commercial scale batches in order to bridge to the pilot-scale primary stability batches.

Meeting Discussion: Since the sponsor does not have any (b) (4) *g commercial-scale batch to place on stability, the sponsor will launch the product using the* (b) (4) *g pilot-scale production*

(supported by the available long-term pilot-scale primary stability batches). So in the NDA, the "commercial-scale" production will be the same production used for the pilot-scale primary stability batches. The NDA will include a comparability protocol for the (b) (4) *g scale-up with a request to downgrade the supplement category when the supplement will be submitted for the* (b) (4) *g scale.*

2.3 Nonclinical

Question 16: Does the Agency agree that no additional nonclinical studies are needed to support a 505(b)(2) NDA for the drug/device combination product AMG504-1 Glucagon Nasal Powder?

FDA Response to Question 16:
No, we disagree. A comparative bridging toxicity study with a U.S. approved glucagon product is needed to qualify any differences in impurity, degradant and safety profiles for the NDA. Additionally, the quality of the published literature you plan to submit in support of your 505(b)(2) application will be a review issue.

Meeting Discussion:
The Agency commented that a nonclinical bridging toxicology study to a U.S.-approved glucagon product would be necessary to qualify impurities present in the sponsor's drug product. The sponsor stated that un-submitted data support that the impurity profile of AMG504-1 is equivalent to the approved glucagon product, and would submit these data to support that a bridging nonclinical toxicology study is not necessary. The Agency agreed to review these data but reiterated that a successful bridge to an approved glucagon product would be required for a 505(b)(2) NDA application.

Post-meeting Comment: You are proposing to use the 505(b)(2) pathway to obtain approval of your product by relying, in part, on FDA's findings of safety and effectiveness for a U.S. approved glucagon product. You need to establish an adequate scientific bridge between your product and a U.S. approved glucagon product to demonstrate that such reliance is scientifically justified. If manufacturing methods result in differences in the impurity profile of your product versus the listed drug that would not support a physico-chemical bridge, then a nonclinical bridging toxicity study may be required. Please refer to the Guidance for industry "Applications Covered by Section 505(b)(2)".

Question 17: Does the Agency agree that no additional nonclinical studies on DPC are needed to support the AMG504-1 505(b)(2) NDA?

FDA Response to Question 17:
Your proposed nonclinical studies for DPC support a 505(b)(2) NDA application; however, review of all final study reports is necessary to confirm exposures in animals (e.g. DPC toxicokinetic data or evidence of lack of absorption), determine appropriate NOAEL(s), and establish relevance to patient risk. Please refer to the Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients.

Reference ID: 4468267

Meeting Discussion: No further discussion.

2.4 Clinical

Question 18: Does the Agency agree that the immunogenicity data will be adequate to support the AMG504-1 505(b)(2) NDA?

FDA Response to Question 18:

We are not be able to make a decision regarding whether the data is sufficient to support the NDA without looking at the complete data from the immunogenicity studies that you are planning to include in your NDA submission. Moreover, we don't have information on the assays that you used to measure anti-drug responses. Your NDA submission should include a description of each assay validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and each assay's SOP, as well as the clinical data on immunogenicity obtained during your clinical trials. Information on the development and validation of assays to assess product immunogenicity may be found in:
Guidance for Industry - Assay Development for Immunogenicity Testing of Therapeutic Proteins (December 2009), as well as several white papers.

Meeting Discussion: No further discussion.

Question 19: Does the Agency agree that the exposure to AMG504-1 is sufficient to support a 505(b)(2) NDA?

FDA Response to Question 19:

The anticipated exposure, including the actual use studies, appears adequate to allow review of the data. The final decision will be made during the review cycle.

Meeting Discussion: No further discussion.

Question 20: Does the Agency agree that the main safety measures in the ISS should be the incidence of treatment-emergent adverse events and the absolute change in the total score of the Nasal and Non-Nasal Questionnaire (occurrence of nasal / non-nasal symptoms)?

FDA Response to Question 20:

Adequate characterization of treatment-emergent adverse events should be a major focus of the ISS. We would consider the Nasal and Non-Nasal Questionnaire to be an additional important component of the integrated safety assessment. We are also interested in how resolution of sign/symptoms were assessed and captured over time (i.e., data on reversibility of symptoms and quality of these data). You should present categorical analyses showing proportion of patients by score categories of increased severity (pre-specify categories and your rationale for selecting these categories). In addition, we request that analyses around nasal/respiratory adverse events, including anosmia, the time needed for resolution be presented as a separate analysis. Clarify which safety data (i.e., vital statistics, laboratory, etc.) you do not intend to include in the ISS and your rationale for not including these.

Meeting Discussion: The sponsor asked for clarification regarding whether the score categories refer to the Nasal and Non-Nasal Questionnaire and the Agency confirmed that this is the case. The sponsor also asked for confirmation that the analyses around nasal/respiratory adverse events refer to treatment emergent adverse events and not the questionnaire. The Agency confirmed that this is the case.

Post-meeting Comment: While we agree that this is acceptable for NDA submission, additional analyses may be requested during the NDA review.

Question 21: Does the Agency agree with the proposed data to be included in the ISS?

FDA Response to Question 21:
You propose to integrate safety data from studies which include 0.5 mg, 1 mg, 2 mg, 3 mg, and 6 mg doses of AMG504-1, but not include data from the actual use studies with the justification that these rely on caregiver and patient reported outcomes. We believe that data from the actual use studies is valuable in the context of a safety analysis and should be included in a separate section of the ISS (i.e., not pooled with the clinic data). Describe how you intend to present safety data from actual use studies (i.e., pooled versus separate) and your rationale. Your proposal to present individual study safety data for the in clinic studies is also acceptable. Clarify your pooling strategy and the rationale for pooling specific studies at the meeting. Clarify whether you will explore/characterize dose response for safety outcomes in your ISS.

Meeting Discussion: The sponsor agreed to present the data from actual use studies as separate clinical study reports and in a separate section of the clinical summaries of efficacy and safety. The Agency agreed with this approach.

Post-Meeting Comment: In a post-meeting communication, you clarified that the planned pooling would be by age groups, and that they would be presented separately. This appears to be a reasonable pooling strategy. You also stated that safety results will be explored by dose administered. This is also acceptable.

Question 22: Does the Agency agree that, in accordance with the agreed SPA and the primary endpoint used in the AMG106 study, the primary endpoint in the ISE should be the proportion of patients in the AMG102 and AMG106 studies achieving either an increase in glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL within 30 minutes after receiving study glucagon, without receiving any other measure to increase the blood glucose level?

***FDA Response to Question 22*: This is acceptable. In the ISE you should also present other efficacy data collected in your trials or justify the rationale for not including these. If you present efficacy analyses in the ISS on endpoints that were not part of the pre-specified statistical analysis plan for the individual study (i.e., not the primary endpoint and no alpha-error control), you should clearly identify these as descriptive only.**

Meeting Discussion: No further discussion.

Question 23: Does the Agency agree that, in accordance with the agreed SPA, the time to achieving either an increase in glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL after receiving study glucagon, without receiving any other measure to increase the blood glucose level (e.g. intravenous glucose, additional glucagon, or exogenous carbohydrates) is a secondary endpoint in the ISE?

FDA Response to Question 23:
This is acceptable. See above comment.

Meeting Discussion: No further discussion.

Question 24: Does the Agency agree that these data are sufficient to support a label indication for use in the pediatric age groups tested?

FDA Response to Question 24:
This will be addressed during the review cycle as it is premature to comment on this until we have fully reviewed the data. As discussed in the End of Phase 2 Meeting, all the data on pediatric patients, including the completed actual use study, will be required to support a pediatric indication. We acknowledge that you submitted PK/PD modeling report during the IND review. We request that you also submit the PK/PD analysis report, model codes, and the associated raw data sets with the NDA for Agency's review. This information will be helpful in understanding the pediatric and adult PK/PD data, and in overall evaluation of the proposed pediatric use of AMG504-1.

Meeting Discussion: No further discussion.

Post-meeting Comment: Please confirm your plan to submit the PK/PD modeling report, codes, and associated raw data sets, as requested in the FDA response above.

Question 25: Does the Agency agree that no further human factors studies are needed to support the AMG504-1 505(b)(2) NDA?

FDA Response to Question 25:
The determination of whether any additional human factors validation studies are needed is a review issue that will be evaluated once you submit the full HF study results report along with your labels and labeling. From the background information provided, it appears that your human factors validation studies are adequate for submission of an NDA.

Meeting Discussion: No further discussion.

Question 26: Does the Agency agree that interim data analysis for the actual use studies (AMG108 and AMG109) can be included in the 505(b)(2) NDA, with a commitment to provide the final data and study reports post approval of the NDA?

FDA Response to Question 26:
For the actual use study, clarify how the number of patients exposed and exposure duration will differ between NDA submission (proposed May 15, 2015, data lock) and final report. Inclusion of interim data from the actual use studies in your NDA submission is acceptable. Final data and study reports will need to be submitted once the studies are complete. We remind you that, as discussed at the End of Phase 2 Meeting, both the in clinic and completed actual use studies will be needed to support a pediatric indication.

Meeting Discussion: The sponsor stated that the expected exposure from Study AMG108 at the time of the NDA submission would be around 75-80 out of the target of 129, and for the pediatric actual use study AMG 109, around 10-15 exposures out of the target of 20. The Agency stated that the interim data from the adult actual use study (AMG108) could be acceptable for the NDA submission, and reiterated that, in order to obtain a pediatric indication for their product, the study AMG109 needs to be completed at the time of the NDA submission. Alternatively, such an indication could be considered through an efficacy supplement submitted after the NDA approval. The sponsor asked whether it would be acceptable to decrease the target pediatric exposure for the study AMG 109 in order to have the completed study at the time of the NDA submission and the Agency clarified that this is not acceptable as this target has been agreed upon in order to satisfy pediatric exposure requirements. The sponsor inquired what type of data from the actual use studies should be part of the NDA submission and the Agency clarified that we would prefer both completed study reports and datasets for the actual use studies if they are available at the time of NDA submission. Otherwise, we would request interim study reports and datasets in addition to discussion of the findings in the summary of safety. In response to a request for clarification on the design of the studies, the sponsor clarified that the design of the actual use studies is open label and that the patients or caregivers will treat hypoglycemia. The patients are allowed to use the currently FDA-approved injectable if they choose to. In response to a question from the sponsor, the Agency stated that no additional study reports or datasets could be submitted for review during the NDA review unless specifically requested by the Agency.

Question 27: Does the Agency agree that all pooled analyses of efficacy of the ISE, including the achievement of either an increase in glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL within 30 minutes after receiving study glucagon and the time to achieving this endpoint (Section 9.4.4), should be descriptive in nature without formal statistical comparison with the comparator treatment?

FDA Response to Question 27:
Yes, we agree.

Meeting Discussion: No further discussion.

Question 28: Does the Agency agree that all pooled analyses of safety of the ISS, including the incidence of treatment-emergent adverse events and the absolute change in the total score of the Nasal and Non-Nasal Questionnaire (Section 9.4.3), should be descriptive in nature without formal statistical comparison with the comparator treatment?

FDA Response to Question 28:
Yes, we agree.
Meeting Discussion: No further discussion.

Question 29: Does the Agency agree that, whereas the primary pooled efficacy analysis of the ISE will be conducted on patients with T1D, a secondary analysis including both T1D and T2D should also be conducted?

FDA Response to Question 29:
Yes, we agree. Even though the sample size is small, we request the summary descriptive statistics also be included for patients with T2DM.

Meeting Discussion: No further discussion.

Question 30: Does the Agency agree that all pooled safety analyses of the ISS should be stratified by adult vs. pediatric patients and AMG504-1 dose?

FDA Response to Question 30:
We are not sure what you mean by "stratified". The pooled safety data should be presented by adult and pediatric patients separately.

Meeting Discussion: No further discussion.

Additional Comments

Combination Product: As noted in your briefing package the glucagon nasal delivery system is a drug-device combination product. As such, it is subject to 21 CFR Part 4 Sub-Part A: Current Good Manufacturing Practice Requirements for Combination Products accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products.

Meeting Discussion: No further discussion.

3.0 PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to

conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

5.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

6.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and

each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature

Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/contract research organization (CRO) inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Items I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in the submission in the format described, the Applicant can identify the location(s) and/or provide link(s) to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (*Technical Instructions: Submitting Bioresearch Monitoring [BIMO] Clinical Data in eCTD Format*).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in the submission, describe the location or provide a link to the requested information).

1. Please include the following information in a tabular format in the original NDA/BLA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal Investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA/BLA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued at each site

3. Please include the following information in a tabular format in the NDA/BLA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated case report form (or identify the location and/or provide a link if provided elsewhere in the submission).

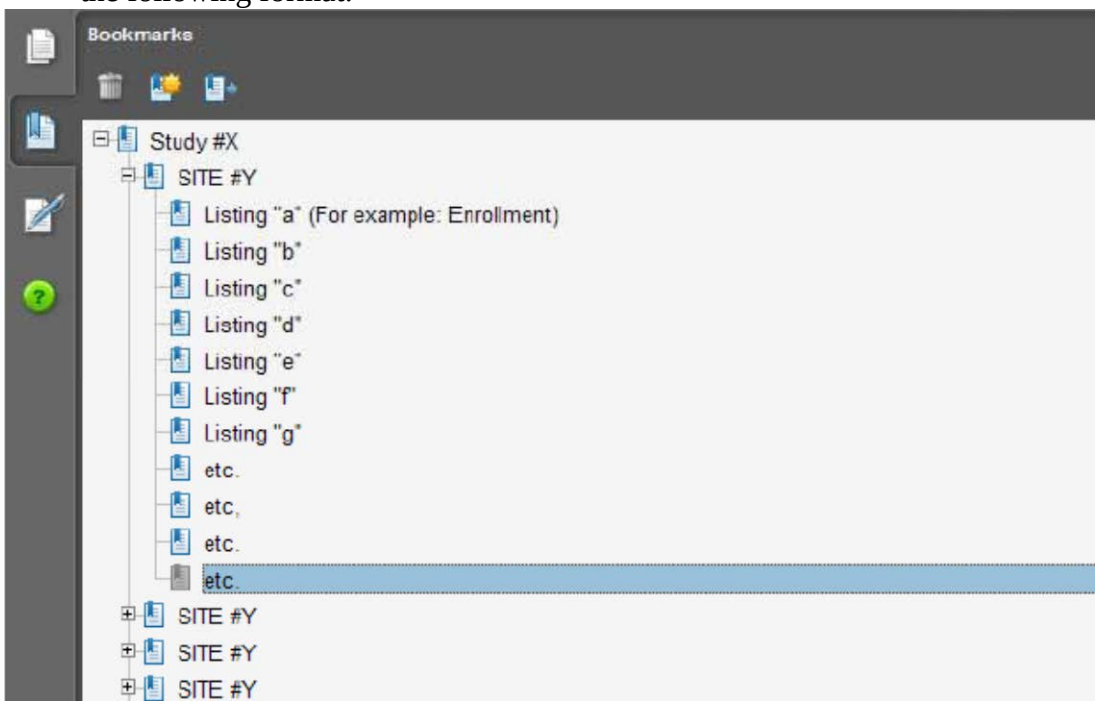
5. For each pivotal trial, provide the original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide:

a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
b. Subject listing for treatment assignment (randomization)
c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per-protocol subjects/ non per-protocol subjects and reason not per-protocol
e. By subject, listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject, listing of AEs, SAEs, deaths and dates
g. By subject, listing of protocol violations and/or deviations reported in the NDA/BLA, including a description of the deviation/violation
h. By subject, listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject, listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject, listing of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

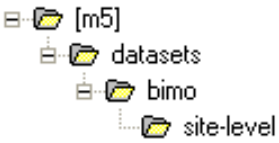
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

OSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

For several of the questions discussed, the sponsor plans to submit additional information to the IND for FDA feedback.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Official Meeting Minutes	FDA	June 5, 2015
Unofficial Meeting Minutes, optional	Locemia Solutions	May 17, 2015
Submit additional data to IND	Locemia Solutions	TBD

6.0 ATTACHMENTS AND HANDOUTS

A table displayed by the sponsor to clarify Question #15 is included below.

Clarification of FDA's comment to Question no. 15

Table 10-40: Revised Overview of Stability Data Available for Filing

Batch	Data available (# of months)	Size	Scale	Use
F121220-001	24	(b) (4)	~~Pilot scale~~ ≥ 1/10 of the target scale	Clinical
F140327-001	12		~~Pilot scale~~≥ 1/10 of the target scale	Clinical
F140423-001	12		~~Pilot scale~~≥ 1/10 of the target scale	Clinical
F141016-001	~~6~~ 9		~~Pilot scale~~≥ 1/10 of the target scale	Clinical
F141113-001	~~6~~ 9		~~Pilot scale~~≥ 1/10 of the target scale	Development
Commitment Batches				
Production batch 1	-		~~Commercial scale~~ Target Scale	Validation[a]
Production batch 2	-		~~Commercial scale~~ Target Scale	Validation[a]
Production batch 3	-		~~Commercial scale~~ Target Scale	Validation[a]

[a] Full manufacturing process validation with (b) (4)

Reference ID: 4468267

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

/s/

JEAN-MARC P GUETTIER
05/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110674

MEETING MINUTES

AMG Medical Inc.
Attention: Claude A. Piché, D.V.M., M.Sc.
Executive Vice-President, Pharmaceutical Research & Development
3780 Mansell Road, Suite T-50
Alpharetta, GA 30022

Dear Dr. Piché:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG504-1 (glucagon) intranasal powder.

We also refer to the meeting between representatives of your firm and the FDA on April 15, 2013. The purpose of the End-of-Phase 2 (EOP2) meeting was to discuss the clinical development plan for AMG504-1 intranasal powder for treatment of severe hypoglycemia (b) (4)

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

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

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Division Director
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:	**End of Phase 2**
Meeting Date and Time:	**April 15, 2013 from 3:00 PM to 4:00 PM**
Meeting Location:	**10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903**
Application Number:	**IND 110674**
Product Name:	**AMG504-1 (glucagon) intranasal powder**
Indication:	**Treatment of severe hypoglycemia** (b) (4)
Sponsor Name:	**AMG Medical Inc.**
Meeting Chair:	**Mary H. Parks, M.D.**
Meeting Recorder:	**Meghna M. Jairath, Pharm.D.**

FDA ATTENDEES

Division of Metabolism and Endocrinology Products (DMEP)
Mary H. Parks, M.D., Division Director
Meghna M. Jairath, Pharm.D., Regulatory Project Manager
Mehreen Hai, Ph.D., Acting Chief, Project Management Staff
Karen Mahoney, M.D., Acting Clinical Team Leader
Suchitra Balakrishnan, M.D., Ph.D., Clinical Reviewer
Karen Davis-Bruno, Ph.D., Non-Clinical Supervisor
Parvaneh Espandiari, Ph.D., Non-Clinical Reviewer

Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Zhihong Li, Ph.D., Clinical Pharmacology Reviewer
Lokesh Jain, Ph.D., Clinical Pharmacology Team Leader

Division of New Drug Assessment III, Office of New Drug Quality Assessment (ONDQA), Office of Pharmaceutical Sciences (OPS)
Joseph Leginus, Ph.D., Chemistry Reviewer
Suong Tran, Ph.D., Chemistry, Manufacturing and Control Lead, Division III

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Alyson Karesh, M.D., Medical Officer
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Office of Pediatric Therapeutics
Michelle Roth-Cline, M.D., Ph.D., Pediatric Ethicist
Robert "Skip" Nelson, M.D., Senior Pediatric Ethicist

SPONSOR ATTENDEES

(b) (4)., Clinical Consultant
Regulatory and Medical Consultant
(b) (4), Consultant in CMC
(b) (4) Consultant in Toxicology
Claude A. Piché, D.V.M., M.Sc., Exec Vice President Pharma R&D, AMG
Patricia Stotland, B.Sc., Director, Regulatory Affairs, AMG

1.0 BACKGROUND

The following background information was retrieved from the background package submitted by the sponsor:

AMG Medical submitted a request for an EOP2 meeting for AMG504-1 (b) (4) nasal glucagon in a (b) (4) powder formulation with dodecylphosphocholine (DPC) and β-cyclodextrin designed for intranasal administration using the (b) (4) nasal dosing device. The sponsor claims that AMG504-1 is a novel, non-injectable glucagon formulation for treatment of severe hypoglycemic reactions, which may occur in the management of insulin treated persons with diabetes mellitus.

This delivery system is designed in a packaging/dosing device intended to allow proper administration in one step.

AMG Medical plans on submitting a 505 (b)(2) New Drug Application (NDA) for AMG504-1, for which the listed products would be GlucaGen (marketed by Novo Nordisk) and Glucagon for Injection (rDNA) (marketed by Eli Lilly).

Regulatory History: The sponsor submitted a Pre- Investigational New Drug (PIND) meeting request on November 26, 2010, which we denied. The sponsor subsequently submitted a new IND on April 5, 2012, which we allowed to proceed after the 30 day safety period. The sponsor submitted the first EOP2 meeting request on July 6, 2012, which we denied and asked the sponsor to provide the full clinical study report (CSR) for the study entitled "A Single Site, Randomized, Three-way, crossover Phase 2 Study To Investigate The Safety And Efficacy Of 2 Dose Levels Of A Novel Glucagon Formulation Compared To Commercially Available Glucagon In Type 1 Diabetic Patients Following Insulin-Induced Hypoglycemia" for our review. The sponsor submitted the full CSR on December 14, 2012.

The sponsor submitted a second EOP 2 meeting request on January 24, 2013, which we granted. The face to face meeting was scheduled for April 15, 2013.

Repeated below in plain text are the sponsor's questions followed by FDA's preliminary responses in bold text. The meeting discussion is in *italics* and the post-meeting note is underlined.

2.0 Sponsor Questions and FDA Preliminary Response

NONCLINICAL

Sponsor Question 1: Does FDA agree that the completed and proposed non-clinical studies on both DPC and AMG504-1 are sufficient, when combined with the known safety of glucagon and beta-cyclodextrin, to support a New Drug Application?

FDA Response: Your nonclinical development plan is reasonable. Characterization of the systemic toxicity of dodecylphosphocholine (DPC) remains outstanding. In the 28-day toxicity studies in the rat (AMG015G) and dog (AMG014G) only the respiratory tissues were assessed for histopathology, although other tissues were collected. Please complete the histopathology on those collected tissue to assess for systemic toxicity. Provide the study reports of AMG 019 & 020 evaluating the toxicity of DPC in the rat by intravenous (IV) administration for review as well.

Meeting Discussion: The sponsor indicated their intention to submit the requested data for FDA review. The sponsor asked about the acceptability of a 505b2 submission using a Lilly manufactured glucagon as the intended listed drug for the nonclinical portion of their development. FDA responded that while this is an acceptable strategy, the AMG glucagon product differs in its route of administration and formulation containing novel excipients (e.g. DPC). The adequacy of the supporting nonclinical data to bridge these differences, including the outstanding need to characterize the systemic toxicity of DPC is a review issue pending submission of the data requested by FDA.

CLINICAL

Sponsor Question 2: Does FDA agree that the primary endpoint (return of blood glucose to the normal range) is appropriate to determine the efficacy of AMG504-1 in the treatment of severe hypoglycemia, and to compare its efficacy with the approved injectable glucagon product?

FDA Response: In principle, proportion of patients with return of blood glucose to the normal range appears to be a reasonable primary endpoint. However it would be clinically relevant only if resolution of hypoglycemia-related clinical symptoms and signs are also assessed. Also refer to our comments for study AMG 106 under Question 3.

The secondary endpoint, time to return of blood glucose to the normal range, is also an important consideration for the overall efficacy assessment.

Meeting Discussion: It was agreed upon that resolution of clinical signs and symptoms will be included. See meeting discussion under question 3.

Sponsor Question 3: Does FDA agree that the proposed clinical development program is acceptable to support approval of AMG504-1 for treatment of severe hypoglycemic reactions?

FDA Response: You are proposing a new route of administration for a medication intended for emergency treatment. Because it is intended to treat serious hypoglycemia, which is a medical emergency, efficacy must be clearly established, and safety must be

adequately characterized. Your study showed that 3 mg intranasal (IN) glucagon has reduced exposure and pharmacodynamic (PD) effects compared to 1 mg subcutaneous (s.c.) glucagon, based on results from your phase 2 study in patients with Type 1 diabetes. In addition, there was a difference in time taken for blood glucose to return to normal range (although small). Therefore, we have some concerns regarding efficacy. Even if number of subjects whose blood glucose returned to normal range was similar between the groups, it is critical that we can be confident about efficacy in patients who experience severe hypoglycemia during usual clinical treatment of diabetes. A circumstance in which glucagon is particularly useful is when the patient's hypoglycemia is severe, with an altered level of consciousness and inability to use oral glucose for treatment. Your proposed clinical development program is very small (only 124 exposed adult patients). A larger program is needed to evaluate the clinical response of patients in the setting of hypoglycemia during usual clinical treatment of diabetes. It is also unknown whether the pharmacokinetic (PK) and PD information obtained during the proposed clinical testing (specifically study AMG106) in conscious patients will fully characterize the effect of nasally administered glucagon in patients with severe hypoglycemia, who often have altered level of consciousness and sometimes have hypotension with shunting of blood flow from the periphery (which may include the nasal circulation) to the central circulation.

Study AMG 106:

- **Because your current study design specifies a target glucose of 3 mmol/L (approximately 54 mg/dl), it is likely that clinical symptoms of hypoglycemia will not occur in all patients. We recommend a lower target glucose (e.g. 2 mmol/L or approximately 36 mg/dL) in study AMG106 so that clinical symptoms are likely to occur and clear evidence of efficacy in treatment of severe hypoglycemia can be assessed. With a target glucose in this desired range, your inpatient clinical center staff will need to be experienced in dynamic endocrine testing procedures and the management of severe acute hypoglycemia. Your protocol will also need to clearly describe procedures for recognizing and treating significant hypoglycemia.**
- **Please calculate the sample size for the primary endpoint. We acknowledge your sample size calculation for the secondary efficacy endpoint based on time to normal blood glucose. However, the primary endpoint is slightly less sensitive than the secondary endpoint and may require additional patients. Also, please justify the non-inferiority margin(s) in the sample size calculations. Type 1 error should be 2.5% one-sided. Consideration should be given to controlling type 1 error across the two efficacy endpoints**

Study AMG 105:

- **If patients on IN glucagon test positive for anti-glucagon antibodies, you will have to develop and validate an assay to detect neutralizing antibodies.**

Study AMG 108:

- **To increase the likelihood that hypoglycemic episodes will occur during the study, we recommend you restrict inclusion criteria to subjects with Type 1 DM.**
- **A larger patient population will be needed.**
- **Include pediatric subjects in this study (see below)**

Pediatric Program:

- **You are proposing to include 18 year-old patients in your pediatric trial (AMG103).**
- **For drug-labeling purposes, pediatric patients are less than 17 years of age. Therefore, although you may include patients 17 years of age and older, you must enroll a sufficient number of younger pediatric patients in your pediatric study to obtain the necessary data for pediatric labeling in the full proposed pediatric age range. See FDA response to Question 4 for further input on your proposed trial, AMG103.**
- **With respect to your proposed User-Friendliness trial (AMG107), your study must include a pediatric "dummy patient" of a variety of apparent ages and weights.**
- **With respect to your proposed Actual Use trial (AMG108), although your current proposal is only for adults, pediatric users, and caregivers of pediatric patients must both be included to gain a pediatric approval of your product.**

Additional Comment:

In your clinical trial protocols, it is stated that blood glucose concentrations will be monitored using a bedside rapid glucose analyzer. Please note that you can use these measurements to ensure patient safety; however, in addition, to support regulatory submission you will also need to measure blood glucose concentrations using a validated bioanalytical method complying with the current bioanalytical standards. Refer to the Guidance for Industry entitled "Bioanalytical Method Validation" for details at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf.

Meeting Discussion:
Further discussion occurred about study designs for 106 and 108:

Study 108:
The sponsor agreed to increase the sample size for study 108 to increase the number of symptomatic hypoglycemic events that are likely to occur. FDA stated that we will need to

review the revised protocol's hypoglycemia event definitions, including those for symptomatic hypoglycemia.

Study 106:
The sponsor indicated that IRB approval to lower subjects to a target glucose of 2 mmol/L (36 mg/dl) might be difficult and proposed a target around 2.5 mmol/L. FDA stated that the goal is to increase the likelihood that symptomatic hypoglycemia (i.e. hypoglycemia with neuroglycopenic signs/symptoms) will occur, and to document that administration of intranasal glucagon reverses the symptoms as well as raises the blood glucose. Lowering the target glucose to 2.5 mmol/L will likely be an acceptable approach to meeting this goal. The revised protocol will need to clearly define the procedures for identifying and treating neuroglycopenic symptoms, and for rescue treatment should intranasal glucagon be ineffective within a time period consistent with protection of study subject safety. Regarding sample size and power calculations, the sponsor was advised to submit a full protocol with detailed rationale for the non-inferiority margins for the primary and secondary endpoints and justification for the expected variability. The clinical meaningfulness will be a review issue and will be discussed further between the statistical and clinical teams. The sponsor was also advised to consider a parallel-group design, instead of a crossover trial, which can be considered due to the need for additional patient exposure.

FDA recommended that the sponsor revise their proposed protocols and resubmit for review, prior to initiating study. The sponsor inquired about how to submit the protocol for review, whether it should be a special protocol assessment (SPA) or just a regular submission. FDA stated that it is up to the sponsor on what route they choose but if they submitted it as a SPA it would have a 45 day review clock. The sponsor had no further questions.

Sponsor Question 4: For use in the pediatric population, the Sponsor is proposing a study in which fasted children and adolescents with T1D are enrolled to evaluate the safety, PK and PD of two dose levels of intranasally administered AMG504-1 compared to injected glucagon.

FDA Response:

Study 103 (also see question 3 for comments about pediatric program):

- **The proposed clinical investigation (AMG103) is approvable under 21 CFR 50.53 as presenting no more than a minor increase over minimal risk, provided that the protocol for monitoring blood glucose during the increase in the basal insulin infusion rate is adequate.**
- **The clear intent is to only enroll children who are well-controlled on insulin pump therapy in order to minimize the risks of the interventions and procedures contained in this clinical investigation. It may be reasonable to add a further inclusion criteria that the subject's HgBA1C is within the**

desired range for age as per current American Diabetes Association (ADA) guidelines.

- **In addition to parental permission, the assent of children greater than 7 years of age should be required for participation in this protocol. An assessment of whether or not children between the ages of 4 to 6 years are capable of assent can be made for each child by the investigator in consultation with the parents.**
- **At least 60% of subjects enrolled should be 4-12 years of age to fully assess PK-PD effects in comparison to adults and variations in absorption in younger populations.**
- **Include hematology and chemistry studies in dosing visits.**
- **We have only reviewed the protocol synopsis, please submit the complete protocol for our review and comments.**
- **You state that the doses for pediatric study are selected based on modeling and simulation. Please submit the datasets and analysis for our review before proceeding with study AMG103.**

Submitting PD data and models:

- **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
- **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps.**
- **For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**

Meeting Discussion: No further discussion.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Sponsor Question 5: Does the FDA agree that the attributes of the drug product AMG504-1, as listed in the specifications, are sufficient to control the quality of the product?

FDA Response: As a preliminary matter, we note that you have stated in the Background section for Q5, "The specifications have been developed based on … FDA's *Draft Guidance: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation, (1998).* The more appropriate Guidance document to consider for your type of drug product is *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation July, 2002.*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidan ces/ucm070575.pdf

The tests included in the drug product specifications appear to be adequate. The following modification to the drug product specifications is recommended:

- **Identification should include testing by two different methods. Although two tests for identification are included in your proposed drug product specifications, both are based on HPLC with UV detection. A second independent test for identification should be included based on a different principle, such as HPLC/MS, SDS-PAGE, amino acid analysis or other orthogonal testing method.**

Evaluation of the data used to establish limits in the drug product specifications will be conducted during the NDA review process.

We remind you that DPC in the drug product formulation is considered a novel excipient. Novel excipients should be appropriately qualified for their intended use. Safety testing of novel excipients is addressed in the FDA's 2005 draft *Guidance for Industry: Nonclinical Studies for Development of Pharmaceutical Excipients.*
http://www.fda.gov/ohrms/dockets/98fr/2002d-0389-gdl0002.pdf
This guidance lists safety-related issues that should be addressed under an IND or NDA in support of proposals to use excipients in new drug products.

Meeting Discussion: No further discussion.

Sponsor Question 6: Does the FDA agree that the attributes related to the drug delivery device (*uniformity of dose delivery, particle size, spray pattern and plume geometry*), as listed in the specifications, are sufficient to control the quality of this component?

FDA Response: As listed in the specifications, testing for uniformity of dose delivery, particle size distribution, spray pattern and plume geometry appear adequate.

We remind you that the design, composition, and quality control of the individual components of the drug delivery device should ensure that the chemical and physical stability of the formulation and performance characteristics of the drug product are maintained.

Specific information for device components should include:

- **Source(s) and fabricator(s) of the overall device**
- **Source(s) and fabricator(s) for each part of the container and closure system**
- **Schematic engineering drawings**
- **Dimensional measurements**
- **Composition and quality of materials**
- **Control extraction studies including toxicological evaluation of the extractables**

Meeting Discussion: No further discussion.

Sponsor Question 7: AMG believes that the (b) (4) should be considered primary packaging, and not a medical device. This is consistent with the classification of Zomig (Astra Zeneca), and Imitrex (GlaxoSmithKline), which are marketed in the United States in liquid spray (b) (4) devices. Does the FDA agree?

FDA Response: We believe that the (b) (4) is a medical device. For the (b) (4) (b) (4) please provide biocompatibility data per ISO 10993-1 as well as physicochemical testing data per USP 661 or an equivalent.

Meeting Discussion: A 510(k) does not need to be submitted for the (b) (4) device.

Post-Meeting Comment: In reference to the medical device, we require the following biocompatibility testing data: cytotoxicity, sensitization (Guinea pig maximization test), and mucosal irritation testing (preferable Syrian hamster pouch test). Alternatively, please provide reference to an FDA cleared device(s) where the same patient contacting materials, from the same material(s) manufacturers, are used in a similar device(s).

Regulatory

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. **In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the**

Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act.
The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	***Nonclinical toxicology***
2. Example: NDA XXXXXX "TRADENAME"	***Previous finding of effectiveness for indication X***
3. Example: NDA YYYYYY "TRADENAME"	***Previous finding of safety for Carcinogenicity, labeling section XXX***

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Additional Comments

Human Factors/Usability

1. In the introductory section of your meeting package, you indicated that your proposed product has been designed to address errors and difficulties observed in the currently available glucagon kit. You also stated that the "ease-of-use of this novel glucagon delivery system is also likely to reduce the burden on physicians and diabetes educators in educating patients…likely to be adopted by emergency care providers…likely to be used by non-medical personnel…" Please note "ease of use" assessments are helpful but do not provide us the necessary evaluation on safe and effective use of the product.

2. Your meeting package does not indicate how you have systematically evaluated use-related risks and how you would validate user-performance based on performance of the highest priority task pertinent to your device through a Human Factors/usability validation study.

i. **Please provide a comprehensive use-related risk analysis for your proposed product. This analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies. We need this information to ensure that all potential risks involved in using your device have been considered and adequately mitigated and the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the device).**

ii. **Please submit your draft Human Factors validation study protocol in advance for us to review in order to ensure that your methods will be acceptable. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.**

iii. **We recommend that you submit the study protocol before submitting your 505(b)(2) application for marketing.**

Meeting Discussion: No further discussion.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).

- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA.

We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.h t m. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There were no pending action items

5.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts.

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

/s/

MARY H PARKS
05/14/2013