

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212097Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115091

MEETING MINUTES

Xeris Pharmaceuticals, Inc.
Attention: Martin J. Cummins
Vice President, Drug Development
3208 Red River Street, Suite 300
Austin, TX 78705

Dear Mr. Cummins:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glucagon, referred to as G-Pen.

We also refer to the meeting between representatives of your firm and the FDA on December 7, 2017. The purpose of the meeting was to discuss the content, organization, and regulatory filing strategy of the G-Pen NDA submission.

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 Petrucci, Regulatory Project Manager at (240) 402-6147.

Sincerely,

{See appended electronic signature page}

Mary T. Thanh Hai, M.D.
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
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: Thursday, December 7, 2:30-3:30pm
Meeting Location: White Oak Building 22, Room 1309

Application Number: IND 115091
Product Name: glucagon
Indication: Treatment of severe hypoglycemia
Sponsor/Applicant Name: Xeris Pharmaceuticals, Inc.

Meeting Chair: William Chong, MD
Meeting Recorder: Marisa Petruccelli

FDA ATTENDEES
Office of Drug Evaluation II

Mary T. Thanh Hai, MD, Deputy Director

Division of Metabolism and Endocrinology Products

William Chong, MD, Clinical Team Leader
Sonia Doi, MD, PhD, Clinical Reviewer
Julie Van der Waag, MPH, Chief, Project Management Staff
Marisa Petruccelli, Project Manager

Office of Pharmaceutical Quality

Suong Tran, PhD, Quality Assessment Lead
Alifiya Ghadiali, PhD, Quality Microbiology Reviewer

Office of Biostatistics

Yun Wang, PhD, Biometrics Team Leader
Anna Kettermann, Dipl. Math, MA, Biometrics Reviewer

Office of Clinical Pharmacology

Manoj Khurana, PhD, Clinical Pharmacology Team Leader
Justin Penzenstadler, PharmD, MS, Clinical Pharmacology Reviewer

Center for Devices and Radiologic Health

Robert Meyer, BS, ME, Reviewer
Carolyn Dorgan, MS, Team Leader

Office of Surveillance and Epidemiology

Susan Rimmel, PharmD, Safety Evaluator, DMEPA
Hina Mehta, PharmD, Team Leader, DMEPA
Naomi Redd, Reviewer, DRISK

Office of Scientific Investigations

Cynthia Kleppinger, MD, Senior Medical Officer

Office of Combination Products

Maryam Mokhtarzadeh, MD, Senior Medical Officer

EUROPEAN MEDICINES AGENCY (EMA) ATTENDEES

Sarin (Sagrario) Rey Torre, PharmD, MSc, Procedure Manager, EMA

SPONSOR ATTENDEES

Martin Cummins, Vice President for Drug Development
Paul Edick, Chief Executive Officer
Ken Johnson, Vice President, Medical Affairs and Quality Assurance
M. Khaled Junaidi, Medical Director, Clinical Research
Anh Nguyen, Medical Director, Strategy & Operations
Steven Prestrelski, Chief Scientific Officer
Poul Strange, Medical Advisor
Michele Yelmene, Regulatory Advisor

1.0 BACKGROUND

The purpose of the proposed meeting is to discuss and reach agreement on the content, organization, and regulatory filing strategy of the G-Pen NDA submission.

The term “G-Pen” has not been reviewed or granted as a proprietary name by FDA. It is used as a developmental designation for convenience.

Xeris Pharmaceuticals has developed a ready-to-use stable liquid formulation of (b) (4) glucagon; currently-marketed forms of this product require reconstitution of lyophilized glucagon in a 9-step process, prior to injection. G-Pen (glucagon injection) is a sterile, subcutaneous injectable, non-aqueous formulation of glucagon. IND 115091 went into effect on September 25, 2013, to allow development of G-Pen as a single-use disposable rescue injection for treatment of severe hypoglycemia in patients with diabetes. Xeris intends to submit an NDA using the 505(b)(2) approval pathway.

G-Pen will be offered in two presentations, a pre-filled syringe incorporated into an auto-injector (Configuration A) and a pre-filled syringe with a manual plunger rod and backstop (Configuration B). The same G-Pen pre-filled syringe is common to both configurations, and will be offered in two fill volumes, 0.5 mg for pediatric patients and 1 mg for patients 12 years and older. Based on available information, these two drug-device configurations are considered combination products under 21 CFR Part 3.

The formulation of G-Pen was modified between Phase 2 and Phase 3 clinical trials (b) (4)

G-Pen has been evaluated in 6 nonclinical studies; 2 non-GLP and 4 GLP studies, and has been evaluated in 4 clinical studies, including a Phase 3 study in adults.

2. DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1: Does the Agency concur with the proposed glucagon drug substance specifications, including the additional acceptance limit of NMT (b) (4)?

FDA Response to Question 1:

The proposed microbiology attributes in the drug substance specification appear adequate.

The proposed regulatory drug substance specification will be evaluated as part of our review of all CMC information in the NDA and comments, if any, will be conveyed to you after our evaluation. Your proposal to have a limit of NMT (b) (4) in the regulatory specification is acceptable; provide a note in the NDA that this limit is lower than the limit in DMF (b) (4) and that the specification in the NDA is the regulatory specification.

Meeting Discussion: After receiving preliminary comments on November 29, 2017, the sponsor asked, via email, for clarification of the reference to ‘microbiology attributes’ in FDA responses to questions 1-3 regarding specifications to understand if FDA meant to indicate acceptance of only the sub-set of microbiology attributes. FDA clarified via email on December 1, 2017, that it meant to indicate acceptance of only the sub-set of microbiology

attributes and that the other attributes in the proposed specifications will be evaluated during FDA review of the NDA, and that a final determination would be based on all information that will be submitted in the application.

Question 2: Both Configuration A and Configuration B of G-Pen utilize an identical primary container closure. Does the Agency concur with the approach to the G-Pen drug product specifications for Configuration A and Configuration B and that they are appropriate to be presented within the same NDA?

FDA Response to Question 2:

The proposed microbiology attributes in the drug product specification appear adequate.

Meeting Discussion: See comment under Question 1.

We concur that the same drug attributes in the drug product specification can apply to both configurations A and B since the two presentations have identical drug formulations.

Additional comments:

We remind you to include in the NDA sufficient information to support the following:

- **proposed acceptance criteria of (b) (4) % for glucagon content (provide clinical information to demonstrate adequate efficacy of both dosage strengths at the lower limit)**

Meeting Discussion: The sponsor presented slide 3 (attached) to give an overview of the trial design for Phase 2 study XSGP-201, which used the original formulation and device Configuration B (pre-filled syringe) and showed that at the end of dosing period (end of clinical trial) the product showed (b) (4) % potency. The sponsor clarified that the (b) (4) % glucagon content specification is for end-of-shelf-life (two years), not release. At manufacturing, the target is (b) (4) %. FDA noted this and commented that the data from the phase 2 study may be adequate to support review and consideration of the proposed end-of-shelf-life acceptance criteria.

- **proposed limit of (b) (4) % on Total Degradants (i.e., provide nonclinical information to qualify this limit)**
- **proposed limit on a specific degradant (i.e., provide nonclinical information to qualify the limits)**

Be advised that referencing the USP monograph alone would not be sufficient information to support the regulatory specification because compendial requirements are minimum quality standards and are not product-specific. In the NDA, provide in tabular format the following information on all product batches used in clinical and nonclinical studies: batch number, clinical or nonclinical study, glucagon content

results (HPLC original, HPLC original-corrected, and UHPLC) and impurities content results (specified impurities and total impurities).

In addition, the device specifications for configurations A and B should be included in the drug product release specifications.

Question 3: Does the Agency concur that the proposed stability program with pre-filled syringes is sufficient to support market authorization of both the Configuration A and Configuration B presentations?

FDA Response to Question 3:

The proposed microbiology attributes in the stability protocol appear adequate. We concur that the same drug attributes and drug-related stability protocol can be used for both configurations A and B since the two presentations have identical drug formulations and primary container closure (prefilled syringe) components, provided that FDA finds the proposed configurations A and B are appropriate for the specific dosing regimen (dose, frequency, and duration).

Meeting Discussion: See comment under Question 1.

Additional comments:

We note that the two clinical batches CMPLI028-16A and CMPLI028-16B will be included in the NDA as two of the six registration batches. Provide confirmation in the NDA that there is no difference between these batches and the commercial product (i.e., no difference in formulation, primary container closure components, or manufacturing facility). In addition, there should be no significant difference in the manufacturing process or scale; tabulate all differences in the manufacturing process or scale and provide bridging data as appropriate.

For device stability, see the response to question 5.

Meeting Discussion: No further discussion.

Question 4: Does the Agency concur that the proposed drug product Extractable/Leachable program is sufficient to support market authorization of both G-Pen Configuration A and Configuration B?

FDA Response to Question 4:

Yes, we concur that the extractable/leachable program used to evaluate Configuration A can be used to evaluate Configuration B since the two presentations have identical primary container closure (prefilled syringe) components. We remind you to provide in the NDA sufficient safety information to qualify any leachable limit/amount present in the product.

A biocompatibility evaluation should be performed on the needle of the pre-filled syringe. In your future marketing application, provide a biocompatibility evaluation of

the needle according to the CDRH guidance, “Use of International Standard ISO 10993-1, ‘Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process’” available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm348890.pdf>.

Meeting Discussion: No further discussion.

Question 5: Does the Agency concur that the proposed reliability testing for G-Pen Configuration B is sufficient to support market authorization?

FDA Response to Question 5:

With respect to the proposed prefilled syringe (i.e., Configuration B), the functional verification summary provided is not considered adequate for demonstrating reliability of the prefilled syringe. The preconditioning (accelerated aging equivalent of expiry, vibration, temperature cycling, and drop) appears acceptable; however the conditions applied should be justified as to how they are representative of a worst case scenario in the full report. It is recommended the conditions are applied sequentially.

In addition to delivered volume, you should verify all essential functions for the combination product, including the following functions:

- Packaging stability
- Needle connections
- Break loose force
- Glide force
- Labeling or marking durability

Additionally, you should support reliability by providing design controls that ensure the proposed products will function as intended. We recommend that the reliability specification for the delivered volume be set at (b) (4) %. In addition, manufacturing controls and processes which are critical to ensuring manufactured products are within specifications should be provided. The design controls and manufacturing controls should be related to a risk analysis, in order to demonstrate all risks are considered while developing the described controls. Finally, you should summarize lot release criteria for the PFS (sample size and features verified).

Additional Comments on Reliability Testing for Proposed Auto Injector:

For agency comments on your reliability proposal for the G-Pen auto-injector, we reference our previous comments in the advice letter dated October 24, 2017. See those comments for testing to support the proposed auto injector.

Meeting Discussion: No further discussion.

2.2. Nonclinical

Question 6: Does the Agency agree that there are no outstanding nonclinical issues regarding glucagon and that the Xeris pharmacology and toxicology studies remain sufficient for filing of both the auto-injector and prefilled syringe presentations of G-Pen?

FDA Response to Question 6:

In general, your nonclinical program appears adequate in scope to support filing a 505(b)(2) NDA. Any impurity or degradant in your drug substance/product should be adequately qualified per ICH Q3A, ICH Q3B, and ICH M7. You should submit adequate safety information to support leachables levels/limits in the product.

Meeting Discussion: No further discussion.

2.3. Clinical

Question 7: Based on the interpretation of results from Study XSGP-301, Xeris intends to submit an NDA for the use of G-Pen (glucagon injection) for the treatment of severe hypoglycemia. Does the Agency agree that Study XSGP-301, the totality of data from the G-Pen development program, and the extensive marketing history of glucagon drug substance are adequate and sufficient to support a filed NDA?

FDA Response to Question 7:

You have completed six nonclinical studies (rats and rabbits), two Phase 2 studies (in healthy volunteers and patients with type 1 diabetes mellitus) and two Phase 3 trials in patients with type 1 diabetes mellitus (one in adults and one in children) to support the use of G-Pen (glucagon injection) for the treatment of severe hypoglycemia.

Overall, we agree that the totality of data for G-Pen is sufficient to support NDA review. However, we have the following comments that should to be addressed prior to NDA submission:

- **Provide clarification as to whether the pharmacokinetics of glucagon was characterized following administration of your glucagon formulation (i.e., G-Pen) 1 mg subcutaneous dose in the Phase 3 study (XSGP-301). If the pharmacokinetics of glucagon following administration of G-Pen via the auto-injector (Configuration A) was not characterized in the Phase 3 study provide an explanation as to how the pharmacokinetics of glucagon following administration of G-Pen via Configuration A and Configuration B will be evaluated. If such information is lacking, we recommend that you conduct a pharmacokinetic/pharmacodynamic study following administration of Configuration A and Configuration B drug products.**

Meeting Discussion: The sponsor presented slide 6 (attached) to show that the same pharmacokinetic (PK) endpoints were collected in the Phase 3 study as in the Phase 2 study. The sponsor added they are still evaluating PK data but that the NDA will include PK data from both study 201 and 301.

FDA elaborated on the reason behind the clarification questions stating that while the information seemed sufficient to submit the application for the autoinjector presentation, the data supporting the prefilled syringe presentation was unclear to the Agency. The Agency further acknowledged that though the container closure is the same in both studies, the final mechanism of delivery is different between autoinjector and prefilled syringe, which could lead to PK/PD differences and needs to be considered.

- **You report that the formulation of G-Pen was modified between Phase 2 and Phase 3 studies. Provide clarification as to how the changes in the formulation of G-Pen impact the pharmacokinetics of glucagon.**

Meeting Discussion: The sponsor presented modifications to the glucagon formulation in slide 10 (attached) and showed the results of a rat study comparing the pharmacokinetics of the two formulations in slide 11. The sponsor added that the Phase 3 formulation used in this study was freshly made, whereas the product used from the Phase 2 formulation was approximately 6 months older.

FDA added that because of device and formulation changes and given the limited animal data pointing to PK differences for the latter factor, it may be challenging to leverage Phase 2 or any other data generated with the manually injected prefilled syringe (Configuration B). The Agency noted that there is uncertainty with regards to the available data supporting Configuration B and emphasized that Xeris would need an adequate scientific bridge to support this presentation. Previous observations of clinical pharmacology data from other products administered via autoinjectors and via manual injection have at times shown differences. A clinical pharmacology bridging study to relate the PK/PD data for the pre-filled syringe to the auto-injector would be the most direct way of addressing this concern.

- **Clarify whether the Phase 2 study (XSGP-201) was conducted following insulin-induced hypoglycemia.**

Meeting Discussion: The sponsor presented slide 8 (attached) to clarify that the Phase 2 study XSGP-201 was conducted after an overnight fast with glucose in range of 80-120 mg/dl at time of dosing.

The sponsor also explained that the potency between the 201 and 301 studies was different due to a change in formulation, which was done to enhance stability.

- **Ensure that information pertaining to the bioanalytical methods used to quantify glucose and glucagon (summary of validation, validation reports, and bioanalytical reports for individual studies) are included in the NDA.**

Please note that in order for us to be able to reproduce your results, at the time of submission, please provide the SAS programs that were utilized to produce all major tables and results for all Phase 3 trials. Please incorporate this information in the

footnote of each table. Also, please include comments and clarifications in your programs codes.

Additional Comments:

You make reference to the extensive marketing history of glucagon to support your proposed NDA. It is unclear what information you are intending to rely upon from previously approved glucagon products. In your NDA submission, you should clearly identify what information you are relying upon.

Question 8: Does the Agency agree that the human factors program for Configuration B will fulfill the NDA filing requirements?

FDA Response to Question 8:

We note that you have already completed a human factors (HF) validation study for Configuration A (autoinjector) and are proposing a HF validation study for Configuration B (prefilled syringe). This approach seems reasonable. However, you have not submitted a comprehensive use-related risk analysis or HF validation study protocol for Configuration B for our review.

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

The risk analysis can be used to inform the design of a HF validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 90 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.

The following items will facilitate an efficient review of your HF study protocol:

- A summary of preliminary analyses and evaluations, including formative studies;
 - Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis
- An updated risk analysis for your product;

- **Detailed HF validation study protocol to include the following elements:**
 - **Description of intended product users, uses, use environments, and training (if applicable) for commercial product**
 - **Graphical depiction and written description of product user interface**
 - **Summary of known use problems with previous models or similar products**
 - **User task selection, categorization (e.g., critical) and prioritization**
 - **Validation testing details**
 - **Objective(s)**
 - **Type of testing (simulated or actual use)**
 - **Test environment and conditions of use**
 - **Training provided to participants and rationale for how it corresponds to real-world training (if applicable)**
 - **Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations**
 - **User tasks and use scenarios that will be studied**
 - **Description of data to be collected and methods for documenting observations and interview responses**
 - **Methods for root cause analysis of all use errors, difficulties, close calls**
 - **Definition of performance success and performance failure**
 - **Moderator transcript**
- **Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study**
- **Five intend-to-market samples of product that will be tested in the HF validation study**

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:

Applying Human Factors and Usability Engineering to Medical Devices, available online at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

Meeting Discussion: No further discussion.

Question 9: Based on Study XSGP-302, Xeris has fulfilled the initial Pediatric Study Plan agreement and proposes to include children 2 years and over in the label population. Does the Agency agree?

FDA Response to Question 9:

It is premature to discuss labeling at this stage. The adequacy of the submitted data to support your proposed indication and population will be assessed during the NDA review.

Meeting Discussion: No further discussion.

2.4. Administrative

Question 10: As the G-Pen development program has demonstrated ease of use (ready to use & easy to administer) as well as efficacy in extreme situations, Xeris intends to request Priority Review for the G-Pen NDA. Does the Agency agree with this proposal?

FDA Response to Question 10:

The determination of whether or not the NDA will be granted a Priority Review will be made after receipt of the NDA.

Meeting Discussion: No further discussion.

Question 11: Does the Agency agree that parallel summaries of efficacy are acceptable and adequate for inclusion in Module 2.7.3?

FDA Response to Question 11:

Your proposed approach to present parallel summaries of efficacy appears adequate for inclusion in Module 2.7.3.

Meeting Discussion: No further discussion.

Question 12: Is the FDA in agreement with proposed placement of the summaries and integrated analyses safety?

FDA Response to Question 12:

Yes, the proposed placement of the summaries and integrated safety analyses appears acceptable.

Meeting Discussion: No further discussion.

Question 13: Does the Agency agree that the size of the overall G-Pen database is adequate to support the filing of both the autoinjector and prefilled syringe NDAs?

FDA Response to Question 13:

See our responses to questions 7 and 8.

Meeting Discussion: No further discussion.

Question 14: Does the Agency agree that the clinical and efficacy data are sufficient to characterize the risk-benefit assessment of G-Pen and that a REMS is not required?

FDA Response to Question 14:

It is acceptable to not propose a REMS at the time of NDA submission. The risk-benefit assessment and the need for a REMS will be determined during the NDA review.

Meeting Discussion: No further discussion.

Question 15: Does FDA agree that all outstanding commitments related to the G-Pen development program have been addressed and that there are none outstanding that would affect the filing of the NDA?

FDA Response to Question 15:

It appears that all the outstanding commitments related to the G-Pen development program have been addressed. However, additional questions or concerns may emerge during the review process which could require additional data.

Meeting Discussion: No further discussion.

COMBINATION PRODUCT - ADDITIONAL FDA COMMENTS:

As noted in the introduction, based on available information, the two drug-device configurations are considered combination products under 21 CFR Part 3.

Location of Combination Product Information:

For information on where to provide device constituent part information using the eCTD format please see eCTD Technical Conformance Guide: Technical Specifications Document: “Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD

Specifications” <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>
(September 2016)

Combination Product Manufacturing:

Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach.

If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR Part 4, see *Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products* (Jan. 2017), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm>.

Information to include in NDA Form 356h: List the manufacturing facilities for the combination product and its constituent parts and identify what activities occur at each site (e.g., assembly, design, filling, sterilization, packaging) involving which constituents parts (e.g., drug only, device only, both drug and device). For facilities that have manufacturing activities for both drug and device constituent parts, you should identify which CGMP operating system is being used at the site for the combination product (streamlined or non-streamlined) and if it is a streamlined system, whether it is a drug-CGMP-based or QS-regulation-based system.

Information to include in your NDA or BLA application. If you are using a drug-CGMP-based operating system, you must demonstrate compliance with the provisions from the QS regulation addressed below. Please provide the information indicated for each requirement unless you are otherwise informed by FDA. Please ensure that the information describes how your firm has applied each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and references to the types of protocols used by your firm for each activity. Using the eCTD format, this information should be provided in Section 3.2.P.3 (for further information, see sec. 5 of eCTD Technical Conformance Guide (Sept. 2016), available at <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>).

- **Management Responsibility (21 CFR 820.20)**

Provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibilities of each facility involved in the manufacturing of the combination product and its constituent parts.

- **Design Control, General (21 CFR 820.30)**

Explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. Please address how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are being satisfied. Provide a copy or a summary of the plan used to design the combination product.

- **Purchasing Controls (21 CFR 820.50)**

Provide a summary of the procedure(s) for purchasing controls. The summary should:

- Describe your supplier evaluation process and describe how it will determine the type and extent of control you will exercise over suppliers.**
- Explain how you maintain records of acceptable suppliers and how you address the purchasing data approval process.**
- Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.**

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreements).

- **Corrective and Preventive Action (21 CFR 820.100)**

Summarize the procedure(s) for your corrective and preventive action (CAPA) system. The CAPA system should require:

- Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;**
- Investigation of nonconformities and their causes;**
- Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and**
- Verification or validation of the actions taken.**

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 (which includes new salts and new fixed combinations), 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 (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP 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 Pedsdrugs@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 [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- 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.
- 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 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

5.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

6.0 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.				

7.0 505(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 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. by 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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 effectiveness 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)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>4.</i>	

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.

8.0 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/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item 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 submission in the format described, the Applicant can describe location or provide a link 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 (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

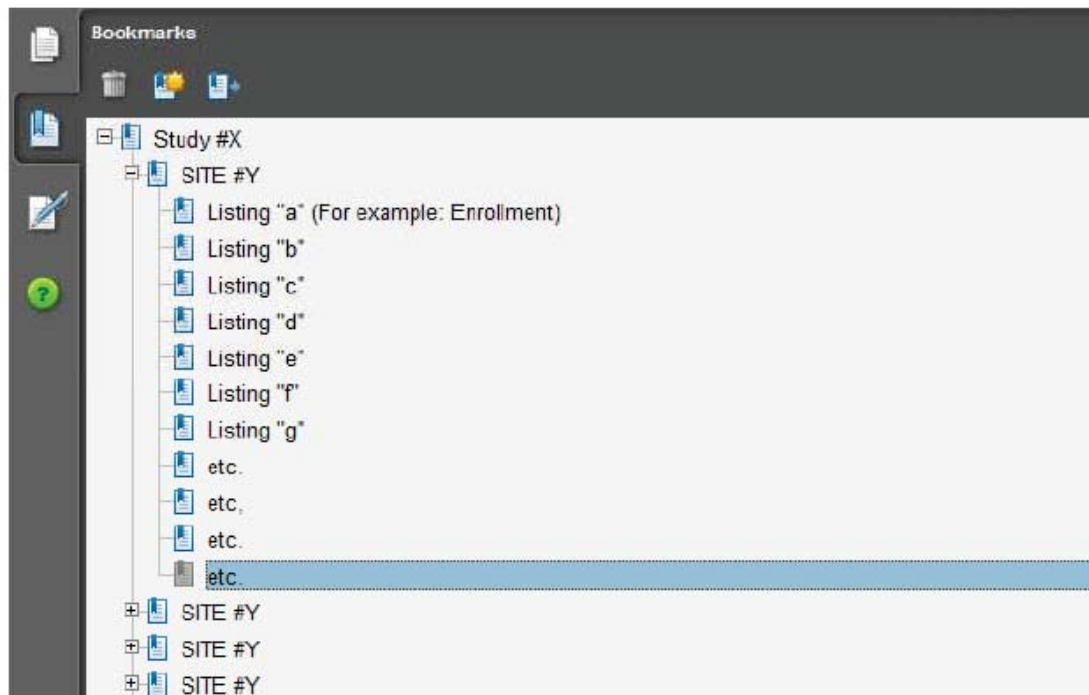
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA 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 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 for each site by site
3. Please include the following information in a tabular format in the NDA 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 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 Organization (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 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 line listings for:
 - 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, 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.

Attachment 1
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.”

DSI Pre-NDA Request Item¹	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:



- 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.

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

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

9.0 ATTACHMENTS AND HANDOUTS

See attached slides provided by the sponsor prior to the meeting.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MARY T THANH HAI
01/03/2018



IND 115091

MEETING MINUTES

PCH Integrated Regulatory Services, Inc.
Authorized Agent for Xeris Pharmaceuticals
Attention: Pauliana Hall, R.A.C.
Regulatory Advisor and FDA Contact
30412 Le Port
Laguna Niguel, California 92677

Dear Ms. Hall:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act on behalf of Xeris Pharmaceuticals for G-Pen (glucagon for injection).

We also refer to the meeting between representatives of your firm and the FDA on July 28, 2014. The purpose of the meeting was to discuss the results of your Phase 2 study (Protocol No. XSGP-201) and your proposed Phase 3 pivotal study (Protocol No. XSGP-301) design and endpoints.

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 Elisabeth Hanan, Regulatory Project Manager, at (240) 402-0350.

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: B
Meeting Category: End of Phase 2

Meeting Date and Time: Monday, July 28, 2014; 2:30 – 3:30 P.M.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 115091
Product Name: G-Pen (glucagon for injection)
Indication: Treatment of severe hypoglycemia
Sponsor/Applicant Name: Xeris Pharmaceuticals (Xeris)

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Elisabeth Hanan, M.S.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director
Jennifer Rodriguez Pippins, M.D., M.P.H.	Deputy Director for Safety (Acting)
William Chong, M.D.	Clinical Team Leader
Suchitra Balakrishnan, M.D., Ph.D.	Clinical Reviewer
Karen Davis-Bruno, Ph.D.	Nonclinical Team Leader
Robert Maher, Ph.D., D.A.B.T.	Nonclinical Reviewer
Julie Van der Waag, M.P.H.	Chief, Project Management Staff
Elisabeth Hanan, M.S.	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Ritesh Jain, Ph.D.	Clinical Pharmacology Reviewer
Jayabharathi Vaidyanathan, Ph.D.	Clinical Pharmacology Reviewer

*Center for Devices and Radiological Health, Office of Device Evaluation,
Division of Anesthesiology, General Hospital, Dental, and Infection Control Devices*

QuynhNhu Nguyen, C.C.	Combination Products Human Factors Specialist
Catherine Li	CDRH Reviewer

SPONSOR ATTENDEES

Douglas Baum, M.S.
Steven Prestrelski, Ph.D., M.B.A.
Brett Newswanger, M.B.A.
Pauliana Hall, R.A.C.

President and C.E.O., Xeris
Chief Scientific Officer, Xeris
Director – Glucagon Products, Xeris
Regulatory Consultant and F.D.A. Contact,
P.C.H. Integrated Regulatory and
Compliance Services

(b) (4)

1.0 BACKGROUND

Xeris has developed a stable liquid glucagon formulation that can be administered as provided; currently-marketed forms of this product require reconstitution of lyophilized glucagon prior to injection. Xeris currently holds (b) (4) active INDs for their glucagon injection formulation, which they plan to submit using the 505(b)(2) approval pathway. The first IND (and subject of the current meeting) is for the G-Pen (IND 115091). The G-Pen utilizes their stable formulation of glucagon for use in a disposable auto-injector for the treatment of severe hypoglycemia. This IND became active on September 25, 2013, following resolution of a full clinical hold. Their Phase 2 clinical trial (Protocol No. XSGP-201) was completed in December 2013; this study compared safety, pharmacokinetics, and efficacy of the G-Pen with Eli Lilly's glucagon for injection.

(b) (4)

The briefing package for this meeting was submitted on June 27, 2014. The Agency issued preliminary comments to the questions contained in this document on July 24, 2014. The sponsor submitted clarifying requests for these responses on July 25, 2014, and proposed a reduced agenda to focus discussion on Questions 1-4, 6, 14, and device comments.

The proposed proprietary names (G-Pen, (b) (4)) have not yet been reviewed.

(b) (4)

2.0 DISCUSSION

The sponsor's questions are repeated below in regular text, followed by the FDA preliminary response (bolded), the sponsor's clarifying requests (italicized), the meeting discussion (bolded/italicized), and post-meeting comments (bolded).

2.1. Clinical

Question 1: In our Phase 2 Protocol No. XSGP-201, as administered from a pre-filled syringe, G-Pen™ (glucagon injection) 1.0 mg demonstrated therapeutic equivalence as compared to Eli Lilly Glucagon [glucagon for injection (rDNA origin)] 1.0 mg, with regard to efficacy parameters $AUC_{(0-\infty)}$ (area under the glucose time curve from $t = 0$ to $t = \infty$) C_{max} (maximum blood glucose concentration), and t_{max} (time to blood glucose maximum concentration) (Section 4.2.1 [of the briefing package]). Therefore Xeris intends to confirm the efficacy of G-Pen™ 1.0 mg dose, same as the approved comparator label dose, in the proposed pivotal study (XSGP-301) (Section 4.4.1 [of the briefing package]).

Assuming the pre-filled syringe in an auto-injector planned to be used in the pivotal study (XSGP-301) will administer the same 1.0 mg dose of G-Pen™ (glucagon injection) as the (b) (4) pre-filled syringe used in Phase 2 study (XSGP-201), does the Agency agree the dose, 1.0 mg, chosen for G-Pen™ (glucagon injection) for the pivotal study (XSGP-301) is appropriate?

FDA Response to Question 1: Your selection of 1.0 mg dose for the pivotal study (XSGP-301) seems appropriate. However, we do not agree with your proposal to demonstrate only the pharmacodynamics (PD) equivalence in your pivotal study. PD for glucagon products may not be a sensitive marker to differentiate between products, as also reflected in your results showing similar PD response for 0.5 mg and 1.0 mg dose in study XSGP-201. Therefore, in your proposed pivotal study you should include both pharmacokinetic (PK) and PD parameters as the main study endpoints. For the test product to be considered equivalent to the reference product, bioequivalence should be demonstrated for both PK and PD AUC and C_{max} parameters. Inability to demonstrate this may require that additional study of your product will be needed to support the application.

Further, we note that the proposed pivotal study evaluates only the subcutaneous (SC) route; therefore, the indication will be restricted to the SC route of delivery. If/when you intend to obtain approval for intramuscular administration, additional information may be needed.

Sponsor's Clarifying Request for Questions 1-4 and 6: The questions listed below were submitted by the sponsor via email on July 25, 2014. These questions were modified in the slides that were supplied on July 28, 2014 (see Section 9.0 below, Attachments and Handouts).

- a) *If our proposed pivotal Phase 3 Study XSGP-301 is modified to evaluate the efficacy and safety of G-Pen in patients in a state of insulin-induced hypoglycemia, "Hypo rescue study", will this study be sufficient (if efficacy and safety is demonstrated) to support the approval of G-Pen for the treatment of severe hypoglycemia?*
- b) *If the answer to (a) is YES, we would like to seek guidance on the design of this "Hypo rescue study". We understand the Agency may not be able comment on any specific questions relating to the "Hypo rescue study" since it has not been reviewed.*

- c) If the answer to (b) is NO, we would like to discuss what other study will be acceptable to demonstrate the clinical utility of G-Pen.

Meeting Discussion for Questions 1-4 and 6: The sponsor opened the meeting with a brief presentation including the background of their company, glucagon development program, and comparison of their G-Pen device and formulation with currently-marketed glucagon rescue kits (See Section 9.0 below, Attachments and Handouts). This presentation included a demonstration of the proposed device.

The Agency stated that the review team had not had sufficient time to review the newly proposed study design; therefore, any discussion at the meeting was to be considered exploratory and further comments would be provided following internal review.

A primary point of consideration concerned the relative benefits of a single-arm, uncontrolled study (as proposed by the sponsor) versus a crossover study design with an active control. It was agreed that a placebo-controlled study would not be ethical for this proposed study design. Additional discussion included topics as listed below.

- a) **Patient inclusion criteria:** The sponsor proposed to include only type 1 diabetics, which the Agency agreed is the more sensitive population. These patients would be expected to have less confounding interference from a counter-regulatory response than would type 2 diabetics. The Agency questioned whether the sponsor would enrich the study population for patients at high risk for severe hypoglycemia; the sponsor did not think that this would be necessary in their trial design. The sponsor questioned whether inclusion of only type 1 diabetics would preclude labeling for use in both type 1 and 2 diabetics. The Agency responded that current labeling for glucagon products does not distinguish between type 1 and 2 diabetics (indication is “for treatment of hypoglycemia”).
- b) **Insulin dosage:** It was discussed whether the dose would be based on weight or based on previous dosing regimen (i.e. total daily dose to include long and short-acting insulins). The sponsor indicated that this would be determined during design of the final protocol in consultation with clinicians having experience with these types of trials.
- c) **Laboratory measurements:** The Agency stated that it was expected that hypoglycemia would be defined in the protocol based on plasma glucose levels as measured by laboratory tests, and that this should include two confirmatory measurements within 5 minutes of each other. The sponsor indicated that they are planning to conduct the study at a clinical center with the capability to perform these measurements at patient bedside. The Agency also stated that the sponsor should plan to include pharmacokinetic measurements in their study due to the use of the new device.
- d) **Neuroglycopenic symptoms:** The need to monitor and/or evaluate these symptoms was discussed. The sponsor stated that they were expecting patients in the trial to reach a mild/moderate hypoglycemic state at ~50 mg/dL plasma glucose and hence not all patients would experience neuroglycopenia.

- e) ***Expected success rate and non-inferiority margin:*** *The rationale behind selection of a presumed 90% success rate was discussed. Additional discussion would be needed to select an appropriate non-inferiority margin in a crossover study design comparing to an approved product. This discussion will occur after the sponsor submits a statistical analysis plan to the agency detailing among other things the assumptions and rationale that went into selection of the non-inferiority margin.*
- f) ***Immunogenicity:*** *It was agreed that immunogenicity testing would not be needed for the current program, which will only include single-dose studies, but may be required for the sponsor's chronic-use programs.*

In addition, the Agency confirmed that it would still consider a 1-mg dose appropriate for the newly-proposed study design. The sponsor's proposed clinical package for their complete NDA submission was also discussed, and the Agency agreed that their overall approach appears reasonable at this stage (including the completed pharmacokinetics and pharmacodynamics studies, human factors study to be completed, and the pivotal Phase 3 trial currently under discussion).

Post-Meeting Comments for Questions 1-4 and 6: The pivotal Phase 3 study should be an active-comparator controlled study evaluating the efficacy and safety of Xeris G-Pen 1 mg versus active comparator, to provide more definitive evidence of efficacy. The primary endpoint should be the proportion of subjects achieving an increase in glucose over 70 mg/dL within 30 minutes of receiving study glucagon and without receiving any other measure to increase the blood glucose levels such as intravenous glucose, additional glucagon, or oral carbohydrates. Other outcomes assessed could include:

- a) Time from treatment to return of blood glucose to >70 mg/dL, and
- b) Safety and tolerability observations, including injection site reactions, nausea/vomiting and recovery from clinical symptoms of hypoglycemia.

The statistical analysis plan should include a justification for the choice of non-inferiority margin.

We will provide additional comments following submission of the complete protocol. We recommend that you submit this protocol for Agency review at least 60 days prior to the planned study initiation.

Question 2: Xeris' pivotal study, Protocol No. XSGP-301 (Appendix 8.2 [of the briefing package]), will be a single-center, double-blind, three-way crossover study designed to evaluate efficacy and safety of 1.0 mg G-Pen™ (glucagon injection) as compared to 1.0 mg Eli Lilly Glucagon in a single cohort of fasted, normal healthy volunteers. 1.0 mg Novo Nordisk GlucaGen® (glucagon for injection [rDNA origin]) will also be examined and compared to both 1.0 mg Eli Lilly Glucagon 1.0 mg and G-Pen™ (glucagon infusion), to support future EMA registration. Endpoints will be related to therapeutic equivalence (blood glucose levels) as well as safety observations between Xeris and Lilly (comparator).

The study will be double-blind. An unblinded pharmacist will prepare the injections, and an unblinded study nurse will administer the G-Pen™ auto-injector and/or Lilly Glucagon pre-filled syringe only, and perform no other study procedures) to ensure both subject and investigator are blinded. All efficacy endpoints are based on quantitative laboratory measurements that do not require qualitative assessment. Further, in the Phase 2 study XSGP-201, no safety differences between the two formulations were observed, such that would require use of a double-dummy.

Does the Agency agree with the design of this study, including the population to be studied, dosage selection, comparators justification, and proposed blinding procedure?

FDA Response to Question 2: Please refer to our response to Question 1.

Sponsor's Clarifying Request for Question 2: See corresponding section below Question 1.

Meeting Discussion for Question 2: See corresponding section below Question 1.

Post-Meeting Comments for Question 2: See corresponding section below Question 1.

Question 3: The primary study endpoint will be therapeutically equivalent efficacy, specifically equivalent $AUC_{(0-\infty)}$ (area under the glucose time curve from $t = 0$ to $t = \infty$), between G-Pen™ (glucagon injection) 1.0 mg and Eli Lilly Glucagon [glucagon for injection (rDNA origin)] 1.0 mg as defined by the 90% confidence interval being contained inside the 80%-125% boundaries.

Does the Agency agree the primary study endpoint is sufficient to establish substantial evidence of efficacy to support the G-Pen™ 505(b)(2) NDA?

FDA Response to Question 3: No we do not agree with relying only on the PD equivalence and using only the $AUC_{(0-\infty)}$ as primary endpoint. Please refer to our response to Question 1.

Sponsor's Clarifying Request for Question 3: See corresponding section below Question 1.

Meeting Discussion for Question 3: See corresponding section below Question 1.

Post-Meeting Comments for Question 3: See corresponding section below Question 1.

Question 4: The secondary efficacy endpoints will be comparable $C_{\max}$ (maximum blood glucose concentration) and $t_{\max}$ (time to blood glucose maximum concentration) between G-Pen™ (glucagon injection) 1.0 mg and Eli Lilly Glucagon [glucagon for injection (rDNA origin)] 1.0 mg.

Does the Agency agree with the choice of secondary efficacy endpoints to show a comparable pharmacologic profile of G-Pen™ and the reference product, Eli Lilly Glucagon, to support the G-Pen™ 505(b)(2) NDA?

FDA Response to Question 4: Please refer to our responses to Questions 1 and 3.

Sponsor's Clarifying Request for Question 4: See corresponding section below Question 1.

Meeting Discussion for Question 4: See corresponding section below Question 1.

Post-Meeting Comments for Question 4: See corresponding section below Question 1.

Question 5: To demonstrate G-Pen™ (glucagon injection) 1.0 mg safety-related parameters are comparable or statistically non-inferior to Eli Lilly Glucagon [glucagon for injection (rDNA origin)] 1.0 mg, Study XSGP-301 will examine the following safety parameters: glucagon exposure levels (area under glucagon concentration vs. time curve), adverse events, 12-lead ECGs, blood pressure, heart rate and clinical laboratory data.

Does the Agency agree the safety parameters monitored and compared in this study are appropriate and sufficient to demonstrate the safety of G-Pen™ to support the 505(b)(2) NDA approval?

FDA Response to Question 5: In addition to the safety-related parameters proposed, injection site pain/reactions should be closely monitored.

Sponsor's Clarifying Request for Question 5: None.

Meeting Discussion for Question 5: None.

Post-Meeting Comments for Question 5: None.

Question 6: Based on the Pre-IND guidance, FDA agreed the proposed Phase 3 Protocol XSGP-301 will be the only pivotal clinical study required for NDA registration (Appendix 8.2 [of the briefing package]).

Does the Agency agree that if the primary efficacy and safety of G-Pen™ (glucagon injection) 1.0 mg is demonstrated in Study XSGP-301, it will be sufficient to provide the necessary evidence of efficacy and safety to support the approval of G-Pen™ for treatment of severe hypoglycemia?

Does the Agency agree the clinical studies presented in Appendix 8.4 [of the briefing package] are sufficient to support the G-Pen™ 505(b)(2) NDA submission?

FDA Response to Question 6: Please refer to our response to Question 1.

Sponsor's Clarifying Request for Question 6: See corresponding section below Question 1.

Meeting Discussion for Question 6: See corresponding section below Question 1.

Post-Meeting Comments for Question 6: See corresponding section below Question 1.

Question 7: Xeris does not intend to change the currently labeled pediatric rescue dose (0.5 mg) as per the Lilly comparator, and will develop a second auto-injector product that will administer a 0.5 mg dose of G-Pen™ (glucagon injection). This 0.5 mg presentation will require additional CMC development work on the auto-injector and require manufacturing separate batches of drug product. As such, Xeris proposes completing the 0.5 mg G-Pen™ CMC development and initiating a pediatric clinical study after the initial NDA approval of the G-Pen™ 1.0 mg product for adult indication. Xeris will submit the Pediatric Study Plan within 60 days following the End-of-Phase 2 meeting. Does the Agency agree with this proposal?

FDA Response to Question 7: The proposal to submit the initial Pediatric Study Plan within 60 days following the End-of-Phase 2 meeting is acceptable.

Sponsor's Clarifying Request for Question 7: None.

Meeting Discussion for Question 7: None.

Post-Meeting Comments for Question 7: None.

2.2. Nonclinical

Question 8: A 14-day study in rats comparing Xeris G-Pen™ (glucagon injection) with Lilly Glucagon [(glucagon for injection (rDNA origin))] at the same three doses demonstrated no significant toxicological effects in either drug product and no difference in the observed pharmacodynamic profiles up to a 20-fold margin above the human equivalent dose (HED) (Section 5.2.1.1 [of the briefing package]). We believe comparable nonclinical safety of the two products has been demonstrated, additional toxicology studies would not be necessary to support the G-Pen™ 505(b)(2) NDA.

Does the Agency agree the nonclinical studies described in Appendix 8.3 [of the briefing package] are sufficient to support the G-Pen™ 505(b)(2) NDA submission?

FDA Response to Question 8: Yes, the nonclinical studies described in Appendix 8.3 of the briefing package are sufficient to support the acute subcutaneous use of the G-Pen (glucagon injection) for the G-Pen 505(b)(2) NDA.

Sponsor's Clarifying Request for Question 8: None.

Meeting Discussion for Question 8: None.

Post-Meeting Comments for Question 8: None.

Question 9: As part of the same 14-day study in rats, the G-Pen™ (glucagon injection) excipients, DMSO and trehalose, were also dosed up to a 20-fold margin above the HED (Section 5.2.1.1 [of the briefing package]). The study successfully demonstrated no significant toxicological effects or differences as compared to the reference product, Eli Lilly Glucagon. Therefore this study also qualified the excipients used in the G-Pen™ formulation.

In addition, a literature search shows G-Pen™ excipients (DMSO and trehalose) are either on the FDA Inactive Ingredients Guide (IIG) or being used in FDA approved products at higher doses than those being administered by G-Pen™.

There is no plan to change the G-Pen™ formulation in the to-be-marketed product. We believe the safety of DMSO and trehalose has been established in our completed studies and is supported by the safe use in approved pharmaceutical products (Section 5.2.2 [of the briefing package]).

Does the Agency agree that the nonclinical studies conducted by Xeris together with the published literature and post-marketing experience of pharmaceutical products containing DMSO and trehalose support the safety of these excipients and justify their use in the G-Pen™ commercial formulation without further toxicity studies?

FDA Response to Question 9: Yes, the nonclinical studies described in Appendix 8.3 and published literature described in Section 5.2.2 of the safety of excipients, DMSO and trehalose, in the briefing package appear sufficient to support the acute subcutaneous use of the G-Pen (glucagon injection) for the G-Pen 505(b)(2) NDA.

It will be unlikely that the nonclinical program for acute use of G-Pen in IND 115091

(b) (4)

Sponsor's Clarifying Request for Question 9: None.

Meeting Discussion for Question 9: None.

Post-Meeting Comments for Question 9: None.

2.3. Product Labeling

Question 10: Upon successful outcomes in our proposed clinical development plan, to include a single Phase 3 pivotal study in healthy subjects as described above, we intend to use the appropriate sections of the Eli Lilly Glucagon [glucagon for injection (rDNA origin)] labeling to support the G-Pen™ (glucagon injection) labeling. The current Lilly labeling includes instructions for patients to use 1.0 mg (1 unit) for adults and 1/2 the adult dose (0.5 mg) [0.5 unit] for patients weighing less than 44 lb (20 kg). As our initial NDA approval is for the adult indication, the G-Pen™ labeling would only include instructions for patients over 44 lb (20 kg) to use the 1.0 mg (1 unit) G-Pen™ auto-injector to treat severe hypoglycemia. It is our plan to include the labeling instruction for patients weighing less than 44 lb (20 kg) at post-approval, after successful completion of a pediatric study, followed by a pediatric efficacy supplement (sNDA).

Does the Agency agree with the proposed G-Pen™ dosing instructions presented in Section 6 [of the briefing package]?

FDA Response to Question 10: It is premature to discuss product labeling at this time. The proposal to submit labeling instruction for patients weighing less than 44 lb (20 kg) post-approval with an efficacy supplement, after completion of a pediatric study is acceptable.

Sponsor's Clarifying Request for Question 10: None.

Meeting Discussion for Question 10: None.

Post-Meeting Comments for Question 10: None.

Question 11: In our pivotal study (Protocol No. XSGP-301), the subcutaneous tissue on the upper arm will be used as the injection site to standardize the dose administration procedure. As indicated in the Lilly Glucagon labeling, other subcutaneous tissue, i.e., abdomen or thigh, are also suitable locations for injection. We don't expect there will be any difference in glucagon absorption due to different injection sites and to be consistent with the Lilly labeling, we plan to include other injection sites in the G-Pen™ labeling, i.e., any subcutaneous tissue, including upper arm, abdomen, and thigh.

Does the Agency agree with the proposed G-Pen™ labeling regarding injection site location?

FDA Response to Question 11: We agree. However, if/when you intend to obtain approval for another route of administration such as intramuscular administration, additional information may be needed.

Sponsor's Clarifying Request for Question 11: None.

Meeting Discussion for Question 11: None.

Post-Meeting Comments for Question 11: None.

Question 12: Based on the Pre-IND guidance, G-Pen™ (glucagon injection) can be submitted as a 505(b)(2) NDA, the G-Pen™ labeling (Appendix 8.1 [of the briefing package]) can reference all relevant sections/label text (Section 6 [of the briefing package]) of the Eli Lilly [glucagon for injection (rDNA origin)] labeling. Our proposed G-Pen™ labeling and the approved Lilly labeling is presented in Section 6 [of the briefing package] for comparison.

Does the Agency have any comments or guidance in our proposed labeling for G-Pen™?

FDA Response to Question 12: It is premature to provide comments regarding product labeling at this time. This will be addressed when you submit the proposed labeling with the NDA.

Sponsor's Clarifying Request for Question 12: None.

Meeting Discussion for Question 12: None.

Post-Meeting Comments for Question 12: None.

Question 13: The current Lilly Glucagon labeling does not follow the FDA Physicians Labeling Rule (PLR) guidance. Will this exception apply to the G-Pen™ labeling (Appendix 8.1 [of the briefing package])?

FDA Response to Question 13: No, the prescribing information (PI) submitted with your NDA must conform to the content and format regulations found in 21 CFR 201.56(a) and (d) and 201.57.

Sponsor's Clarifying Request for Question 13: None.

Meeting Discussion for Question 13: None.

Post-Meeting Comments for Question 13: None.

2.4. Human Factors and Usability

Question 14: Under the guidance of Dr. Tony Andre, Xeris will conduct a systematic human factors and usability program to support G-Pen™ auto-injector product registration, as described in Section 4.4.2 [of the briefing package]. Xeris plans to submit the Validation Study Protocol via a SPA for FDA review before the study is conducted.

Does Agency have any comments on the overall design of the human factors study plan?

FDA Response to Question 14: You should note that to be eligible for a Special Protocol Assessment, a clinical protocol must form the primary basis of an efficacy claim. Refer to the FDA Guidance for Industry, “Special Protocol Assessment,” for more information (available online at <http://www.fda.gov/downloads/Drugs/Guidances/ucm080571.pdf>).

Your approach to validate the device user interface seems reasonable. To ensure your approach and methodology are acceptable, please submit your risk analysis and summative human factors (HF) study protocol for review prior to study implementation for Agency review and comment. Ensure that your summative HF study protocol includes summary information from formative HF studies.

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>

Sponsor’s Clarifying Request for Question 14: When should we submit our Risk Analysis and Summative Human Factors study protocol for review, i.e., 60 days, prior to study initiation? Should this submission be sent to CDRH separately? If yes, who will be our CDRH contact for G-Pen?

Meeting Discussion for Question 14: *The Agency stated that the protocol should be submitted to DMEP as an amendment to the IND file; DMEP will coordinate with CDRH for review of the protocol. The Agency also stated that the timeline for review needed to be confirmed with CDRH and would be included as a post-meeting comment.*

Post-Meeting Comments for Question 14: We recommend that you submit your HF study protocol for review at least 75 days prior to study initiation. We recommend that you perform the HF study prior to initiating the Phase 3 clinical trial to ensure that the device-user interface has been validated prior to introducing it into the conditions of the clinical trial.

2.5. NDA Contents and Submission Timeline

Question 15: Based on the NDA-related regulatory activities and submissions summarized in Section 7 [of the briefing package], does the Agency have any comments on the activities and their timing proposed for the G-Pen™ NDA program?

FDA Response to Question 15: Your overall timeline appears reasonable. Refer to our responses to Questions 7, 14, and 16, and to our comments listed below.

- a) A pre-NDA meeting should be held at least 2 months before NDA submission. Top-line results from your pivotal study should be available at the time that you submit your request.
- b) We recommend that you submit your request for a small business user fee waiver at least 4 months before NDA submission. Note that you may need to resubmit your request for a waiver in the event that your NDA is submitted more than 1 year after a waiver is granted, or if the NDA is refused to file or withdrawn before filing. For more information, refer to the FDA Guidance for Industry, “User Fee Waivers, Reductions, and Refunds for Drug and Biological Products,” for more information (available online at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079298.pdf>).

Sponsor’s Clarifying Request for Question 15: None.

Meeting Discussion for Question 15: None.

Post-Meeting Comments for Question 15: None.

Question 16: Since G-Pen™ shows promise in treating a serious or life-threatening disease and addresses an unmet medical need, we are seeking Fast-Track Designation status for G-Pen™. If Fast Track Designation is granted, we plan to submit completed sections of the G-Pen™ NDA for review by FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed. Does the Agency agree with our proposed NDA submission plan as outlined in Section 7 [of the briefing package]?

FDA Response to Question 16: The proposed NDA submission plan appears to be based on the premise that you will be able to submit parts of the NDA for review before the complete NDA application is ready. It would be more appropriate to plan to submit a complete application when it is ready for review. If you intend to seek Fast Track Designation, this request will need to be submitted for consideration and you should not assume that it will be granted.

Sponsor’s Clarifying Request for Question 16: None.

Meeting Discussion for Question 16: None.

Post-Meeting Comments for Question 16: None.

2.6. Additional Comments - Device

Within your background document, you reference the “G-Pen” as an auto injector type device. Your submission does not appear to provide a description of this device component, nor does it provide a description of the types of information your firm expects to submit to substantiate device safety as part of a future IND intended to study the drug-device combination product.

In addition to submitting information regarding the human factors/usability of the device, you will need to submit information which substantiates safe use of the device constituent parts of the product as part of a future IND. Information expected to support safe use of the device includes, but may not be limited to:

- a) A detailed description of the device including engineering drawings and diagrams. If your device uses any electrical or software controls, be sure to include these attributes within your description. Additionally, the description should include a listing of all components, subassemblies, and materials used within the device.
- b) A description of device requirements and specifications which are relevant to the functionality of the device under the clinical study.
- c) Information, including test reports, which verify that the essential device characteristics, derived from requirements and specifications, have been satisfied. Such information should substantiate that the device will deliver medication accurately and reliably. The Agency has recognized standards within the ISO 11608 suite which are relevant to the device, as described. Recognized standards can be located at:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>
- d) Information which substantiates that the portions of the device which contact the patient’s tissue have been found to be biocompatible. The Agency has recognized standards within the ISO 10993 suite which are relevant to device biocompatibility.
- e) A description of how the device will be sterilized, packaged, shipped to the clinical site for use, and stored as well as information which validates the device will be safe for use after these activities.

Sponsor’s Clarifying Request for Device Comments: We are planning to have a separate CMC EOP2 Meeting to discuss our CMC plan for the G-Pen formulation and the auto-injector device (“(b) (4)” auto-injector) to be used in Phase 3 and as the commercial G-Pen product. Pre-marketing clearance of the (b) (4) auto-injector has not been obtained and currently there are no pharmaceutical products approved using the (b) (4) device. We propose to include a detailed description of the (b) (4) device as outlined in subsections i-v

under 2.6 Additional Comments-Device in an upcoming CMC Information Amendment for the Division and CDRH review prior to our CMC EOP 2 Meeting. Is our plan acceptable?

We would like clarify the Agency comment concerning a future IND in the second paragraph under 2.6 Additional Comments-Device. Please note we are NOT planning to file a new IND for the (b) (4) auto-injector. As indicated earlier, we are planning to file a CMC Amendment to the G-Pen IND in preparation of the Phase 3 pivotal study and an EOP 2 CMC Meeting. Final G-Pen (b) (4) device design and formulation information will be part of the future G-Pen NDA. Is our approach consistent with the Agency requirement?

Meeting Discussion for Device Comments: *The Agency stated that the regulatory approach proposed by the sponsor as outlined above is acceptable.*

Post-Meeting Comments for Device: None.

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. 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 Pediatric and Maternal Health Staff 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 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>

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

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)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

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 ISSUES REQUIRING FURTHER DISCUSSION

The final study design for the Phase 3 pivotal trial will be discussed following submission of the complete protocol. Details of the G-Pen device design and testing will be discussed at the CMC End-of-Phase 2 meeting.

8.0 ACTION ITEMS

The sponsor will submit protocols for their Human Factors study and Phase 3 pivotal study for Agency review. Timelines for these submissions are recommended in the post-meeting comments for Questions 1 and 14, respectively. In addition, the sponsor will submit an initial Pediatric Study Plan for Agency review within 60 days of this meeting (see our response to Question 7 above and Section 3.0, PREA Requirements).

9.0 ATTACHMENTS AND HANDOUTS

The attached slides were provided by the sponsor via email on July 28, 2014, prior to being presented at the meeting that day.

27 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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
08/27/2014