# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210605Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210605

**REFUSAL TO FILE**

Mylan GmbH
Attention: Suzanne Kiani
Senior Director, Regulatory Science, Biologics
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Kiani:

Please refer to your New Drug Application (NDA) dated and received April 27, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin glargine injection 100 units/mL.

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

The NDA is incomplete because it does not on its face contain information required under section 505(b) of the FDCA and 21 CFR 314.50 (see 21 CFR 314.101(d)(3)).

Specifically, you have submitted a 505(b)(2) application for the proposed to-be marketed insulin glargine product manufactured using Process VI at a facility in Malaysia (i.e., Process VI product), while the insulin glargine product studied in the Phase 3 clinical trials was manufactured using Process V at a different facility in India (i.e., Process V product). We consider the manufacturing change to be a major change.

Based on the specific manufacturing changes made, additional clinical safety and efficacy bridging data, including an assessment of immunogenicity, are needed to establish that the efficacy and safety data generated with Process V product (i.e., Phase 3 product) is relevant to Process VI product and can be used to support a determination that the proposed to-be marketed product (i.e., Process VI product) is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus.

In Study MYL-1501D-1001, only $AUC_{0\text{-}24h}$, a pharmacokinetic endpoint, was used as the primary endpoint and pharmacodynamic (PD) endpoints were considered secondary. PD endpoints, such as $AUC_{GIR0\text{-}24h}$, are important endpoints when comparing across insulin glargine products, and are generally used as additional primary endpoints in comparisons. In Study MYL-1501D-1001, PD similarity was not demonstrated for $AUC_{GIR0\text{-}24h}$, $AUC_{GIR0\text{-}12h}$, and

$AUC_{GIR12-24h}$ between Process V product (i.e., Phase 3 product), and Lantus. Differences in PD endpoints were also noted across other comparisons ($AUC_{GIR0-12h}$, and $AUC_{GIR12-24h}$) between Process V and VI products.

While the following are not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

**Biostatistics**

1. The submission did not include subgroup analyses of safety and effectiveness by gender, age, and race that are required by FDA regulations (21 CFR 314.50).

**Drug Substance**

2. To be consistent with the USP Monograph for Insulin Glargine which includes meeting the requirements for Insulin Assay, Bioidentity Test <121>, revise the MYL-1501D drug substance specifications to include this test. We do not agree that an RP-HPLC assay can be substituted for a bioassay as part of the specifications for the MYL- 1501D drug substance. We remind you that in the April 4, 2014, End-of-Phase 2 Meeting Minutes for IND 105279 for your insulin glargine injection product, the Agency recommended to, "Add a bioassay to the drug substance specification, and provide data to support the correlation of 0.0364 mg of insulin glargine being equal to 1 Unit of insulin glargine," (p. 5). Further, during this meeting, the Sponsor discussed that "A bioassay based on USP <121> will be included in the drug substance specification," (p. 6).

3. A USP Insulin Glargine Reference Standard is available and should be used going forward as a reference standard for the MYL-1501D drug substance and drug product. In support of the change to the USP standard, provide data comparing the USP Insulin Glargine Reference Standard and the Insulin Glargine EPCRS (European Pharmacopoeia Chemical Reference Substance) that is currently used to qualify the working standards.

**Drug Product**

4. Regarding your drug product specification, we have the following comments.
    a. Provide an assessment of how your test methods and acceptance criteria proposed for drug product comply with the USP insulin glargine injection monograph.
    b. For those methods which are not aligned with the USP insulin glargine injection monograph, provide data to support the equivalency of your analytical methods to those in the USP insulin glargine injection monograph. Refer to comment #4 (Drug Substance).
    c. We note that your RPUPLC potency assay uses a single standard to calculate the potency of an unknown sample, whereas the USP monograph for Insulin Glargine Injection requires the construction of a calibration curve based on three standards used for the test. Justify your choice of the single standard.

d. Revise your specification to include an acceptance criterion for the color and clarity of the drug product solution packaged in vials and cartridges. Include appropriate reference standard for testing (e.g., Ph. Eur. 2.2.1 and 2.2.2).

e. Insulin glargine content in the drug product should be specified in mg/mL as well as in Units /mL.

5. The expiration dating period and in-use shelf life for the product will be based on real-time stability data and in-use stability data for the combination product.

6. Provide information on the apparent weight-average molecular weights and hydrodynamic radii of insulin glargine in your drug product in comparison to Lantus based on Static or dynamic light scattering studies.

7. Provide the projected environmental assessment (EA) calculation information for the expected levels of your product introduced into the aquatic environment.

**Drug Process:**

8. Please submit the Executed Batch Manufacturing Record of the drug product lots manufactured at Bangalore, India, which were used in the Phase 3 clinical studies (study number MYL-GAI-3001, MYL-GAI-3002).

9. Since the stability of this drug product is temperature dependent, please provide the following information:
   a. Define the manufacturing environmental condition.
   b. Define the time limit for exposure of product to ambient temperature (below 30°C) during manufacturing operation and justify your proposed limit.
   c. Define the hold time and storage condition for process intermediates and the total processing time during the drug product manufacturing process, and provide justification.
   d. Update Module 3.2.P.3.4 with the information requested above.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

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

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting (see 21 CFR 314.101(a)(3)).

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you

requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

**PROPOSED PROPRIETARY NAME**

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, call Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely yours,

*{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

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

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/s/

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JEAN-MARC P GUETTIER
06/26/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105279

**MEETING MINUTES**

Mylan GmbH
Attention: Felix Siegel, Ph.D.
Senior Director, Head of Regulatory Affairs, Biologics
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Dr. Siegel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for insulin glargine injection (rDNA Origin), 100 IU/mL.

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2014. The purpose of the meeting was to discuss regulatory, device, nonclinical, and clinical requirements to support further development.

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 Richard Whitehead, Regulatory Project Manager at (301) 796-4945.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.
Director (Acting)
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:** | Friday, March 7, 2014, 1-2PM |
| **Meeting Location:** | 10903 New Hampshire Avenue<br>White Oak Building 22, Conference Room: 1309<br>Silver Spring, Maryland 20903 |
| **Application Number:** | 105279 |
| **Product Name:** | insulin glargine injection (rDNA origin) 100 IU/mL |
| **Indication:** | long- acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus |
| **Sponsor/Applicant Name:** | Mylan GmbH |
| **Meeting Chair:** | Jean-Marc Guettier, M.D. |
| **Meeting Recorder:** | Richard Whitehead, M.S. |

**FDA ATTENDEES**

Office of New Drugs, Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Director (Acting)
Ali Mohamadi, M.D., Clinical Team Leader (Acting)
Hyon Kwon, Pharm.D, M.P.H., Clinical Reviewer
Miyun Tsai-Turton Ph.D., Nonclinical Reviewer
Karen Davis Bruno, Ph.D., Nonclinical Team Leader
Richard Whitehead, M.S., Regulatory Project Manager
Pamela Lucarelli, Chief Project Management Staff

Office of Biostatistics

Mark Rothmann, Ph.D., Biostatistics Team Leader
Jennifer Clark, Ph.D., Biostatistics Reviewer

Office of Clinical Pharmacology
Lokesh Jain, Ph.D., Clinical Pharmacology Team Leader
Suryanarayana Sista, Ph.D., Clinical Pharmacology Reviewer
Manoj Khurana, Ph.D., Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment (ONDQA)
Su Tran, Ph.D., Product Quality Team Leader

Office of Combination Products
Patricia Love, M.D., MBA, Deputy Director
Bindi Nikhar, M.D., Associate Director

Center for Devices and Radiological Health (CDRH)
Catherine Li, M.S., Combination Products Reviewer
QuynhNhu Nguyen, M.S., Combination Products Human Factors Specialist
Patricia Beaston, M.D., Ph.D., Medical Officer

Office of Biotechnology Products
Daniela Verthelyi, Ph.D., Primary Reviewer

Division of Medication Error Prevention and Analysis
Sarah Vee, Pharm.D., Primary Reviewer

Office of Regulatory Policy
Janice Weiner, J.D., M.P.H., Senior Regulatory Counsel

**SPONSOR ATTENDEES**

Abhijit Barve, President, Research & Development and Regulatory Sciences, Biocon
Andrea B. Miller, Sr. Vice President, Global Complex Products Operations, Mylan
Bin Sun, Senior Lead Biostatistician, Mylan
Brian Stone, Global Counsel, Regulatory Affairs, Mylan
Felix Siegel, Sr. Director, Regulatory Affairs, Mylan
Jeffrey Smith, Vice President Pharmacology and Toxicology, Mylan
Libbie Mansell, Vice President, Regulatory Strategy, Biogenerics, Mylan
Michael Ankersen, Clinical Project Lead – Diabetes, Mylan
Raja Sekhar Reddy Vanga, Assistant General Manager, Regulatory Sciences, Biocon
Rajesh Ullanat, Associate Vice President, Technical Development, Mylan
Ramakrishnan M. S., General Manager, Research & Development, Biocon
Rasmus Rojkjaer, Vice President, Head of Global Biologics R&D, Mylan
Raymond Urbanski, Chief Medical Officer, Mylan
Sunil Jain, Associate Vice President – Program Head Insulin Analogues, Biocon
Walt Owens, Sr. Vice President, Global R&D, Mylan

## 1.0 BACKGROUND

Mylan states that the molecular structure of "Mylan Insulin glargine," solution for subcutaneous injection and Lantus (Sanofi; NDA 21081) is "identical." Mylan states that in both products insulin glargine consists of 53 amino acids arranged in two chains. The A chain (21 amino acids) and the B chain (32 amino acids) are connected by disulfide linkages. There are two differences in the amino acid sequence between human insulin and insulin glargine. The C-terminal of the B chain is elongated by two Arginine residues. The C-terminal Asparagine of the A chain is replaced by Glycine.

The indication and limitations of use are proposed to be the same as that in the labeling of Lantus.

Mylan Insulin glargine is a proposed long-acting human insulin analog for which Mylan is seeking an indication to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM). Important Limitations of Use: Not recommended for treating diabetic ketoacidosis. Use intravenous, short-acting insulin instead.

The dosage form, route of administration and dosing regimen are proposed to be the same as for the listed drug relied upon (US-approved Lantus): Solution for injection 100 units/mL (U-100) in 10 mL vials and 3 mL Mylan pen, disposable insulin device.

Insulin glargine is an analogue of human insulin produced by recombinant DNA technology. Mylan, and its development partner, Biocon Ltd., are proposing to develop this product as a "substitutable, therapeutic equivalent" to Sanofi's Lantus. Lantus was approved on April 20, 2000. There are no currently marketed products identified in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book) as therapeutically equivalent to Lantus, and Mylan states that the availability of a therapeutic equivalent would offer significant public health benefits in terms of patient access and health care cost containment. Biocon was the original sponsor for the referenced IND 105279. In February 2013, Mylan entered a co-development agreement with Biocon for insulin glargine. In August 2013, the sponsorship of the IND was transferred from Biocon to Mylan.

The following list provides an overview of the development program conducted to date to compare Mylan Insulin glargine and Lantus:

1. Physico-chemical characterization includes;
    - Primary structure;
    - Secondary structure;
    - Higher order structures;
    - Impurity profile including RP-HPLC and SEC techniques.

2. Biological characterization includes;
    - Biological activity with respect to glucose uptake, binding to insulin receptor, binding to IGF-1 receptor and cell proliferation in in-vitro studies.

3. Toxicokinetic and toxicology in non-clinical studies;

4. Pharmacokinetic and pharmacodynamic profiles in clinical studies;

5. Clinical effect and safety profile, including immunogenicity, in clinical studies;

6. Same operating principles for Mylan's delivery pen and Sanofi's Solostar.

Mylan intends to seek marketing approval for Mylan Insulin glargine injection under section 505(b)(2) and plans to rely on the Agency's previous finding of safety and effectiveness for the listed drug, Lantus.

The sponsor proposes to conduct two additional supportive clinical studies to confirm the therapeutic equivalence of Lantus and Mylan Insulin glargine:

- A 400-patient 52-week non-inferiority study in T1DM using Mylan disposable pens and Lantus disposable pens. The primary endpoint will be change in HbA1C from baseline at 24 weeks;
- A 500-patient 24- week non-inferiority study in T2DM study using Mylan disposable pens and Lantus disposable pens. The primary endpoint will be change in HbA1C from baseline at 24 weeks.

The purpose of the meeting was to discuss the acceptability of regulatory, CMC, device, non-clinical and clinical proposals to support the therapeutic equivalence of Mylan Insulin glargine to Lantus. In addition, Mylan was seeking concurrence on the design of the clinical studies to ensure data generated from these studies, assuming acceptable results, would be adequate to support product registration.

## 2.0 DISCUSSION

### 2.1 Regulatory

***Question 1:*** Mylan Insulin glargine and Lantus are pharmaceutically equivalent. Bioequivalence was demonstrated in the completed PK/PD study (GLARGCT100111). Through additional studies Mylan will demonstrate that Mylan Insulin glargine and Lantus will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Mylan Insulin glargine and Lantus are therefore therapeutic equivalents (TE).

a. Given the analytical characterization data and completed PK/PD study, does the Agency agree that a 52-week safety, immunogenicity and efficacy study in T1DM patients, in combination with 24-week study in T2DM patients provides sufficient supportive evidence that Mylan Insulin glargine and Lantus will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling along with the completed BE (PK/PD study) and will therefore be considered therapeutically equivalent?

b. With regard to the optional study, does the Agency agree that the proposed 6-month switch extension study (optional study) in T2DM patients as described in Figure 1.6.2-3 is sufficient to provide additional supportive evidence that Mylan Insulin glargine and Lantus are therapeutically equivalent?

c. The formulation of Mylan Insulin glargine is identical to the Lantus formulation in prefilled pens. However, the Lantus vial contains (b) (4) Polysorbate-20, which was not present in the initially marketed Lantus vial product. Does the Agency agree that the slight difference in the formulation of the vial has no impact on the determination of TE?

d. Mylan assumes that, consistent with other TE determinations, a demonstration of TE between Mylan Insulin glargine and Lantus® will be reflected in AB-ratings in the Orange Book. Does the agency agree?

***FDA Response to Question 1:*** **Your questions a, b, and d regarding the criteria for demonstrating therapeutic equivalence between your proposed Mylan Insulin glargine and US-approved Lantus require further internal Agency discussion. Although the background package makes several conclusory statements regarding the "pharmaceutical equivalence" and "bioequivalence" of these biological products, FDA notes that these determinations would be review issues, and the application of these terms to rDNA-derived protein products such as insulin glargine requires additional FDA consideration. Accordingly, while we can provide comments on whether the design of your proposed Phase 3 studies would be adequate to support your proposed 505(b)(2) application, we are unable to comment on whether the design of these studies, in conjunction with other data, would provide adequate data to support a determination of therapeutic equivalence.**

**See our response to Question 9a below, which includes preliminary comments for your proposed Phase 3 studies (MYL-GAI-3001 and MYL-GAI-3002) based on the provided synopsis. Also see our response to Question 9b.**

**With respect to question c, the difference in the formulation of the Lantus vial compared to Mylan's insulin glargine would not be anticipated to impact a determination of TE if this difference does not affect the clinical effect and safety profile. However, this will be a review issue.**

***Question 1 Discussion:*** **The sponsor stated that it would like to continue the dialogue and work with the Agency to develop a product that is demonstrated to be "therapeutically equivalent" to Lantus. FDA reiterated that the approach to and criteria for a demonstration of "therapeutic equivalence" for rDNA-derived protein products such as insulin glargine require further discussion within the Agency.**

***Question 2:*** Mylan intends to obtain marketing approval for Mylan Insulin glargine injection under section 505(b)(2) and plans to rely on the Agency's previous finding of safety and effectiveness for the listed drug, Lantus.

a. Does the Agency agree that no pediatric clinical studies are required to support pediatric dosing?

b. Does the Agency agree that the development of a pediatric formulation is not required?

***FDA Response to Question 2:*** **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.**

**Because none of the criteria apply at this time to your application, your application does not trigger PREA. If there are any changes to your development plans that would cause your application to trigger PREA, your status would change.**

***Question 2 Discussion:*** **No additional discussion.**

### 2.2 Quality

***Question 3:*** Mylan is currently manufacturing Mylan Insulin glargine at a facility located in Bangalore, India. Mylan is in the process of commissioning an additional drug substance (DS) and drug product (DP) manufacturing site in Malaysia to meet the global commercial demand. The three-way toxicity and three-way PK/PD studies were executed using Mylan Insulin glargine manufactured at the facility in India. Mylan Insulin glargine manufactured at the Indian facility will also be used for the planned clinical safety and efficacy studies. Mylan intends to include both facilities, in India and in Malaysia, as commercial manufacturing sites into the marketing application.

a. Does the Agency agree that data generated from clinical and animal toxicity studies for Mylan Insulin glargine manufactured in India in combination with physicochemical and biological data positively demonstrating acceptable comparability for the products manufactured at both sites provided at the time of submission of the marketing authorization are sufficient to support approval of commercial manufacturing in India and in Malaysia?

b. Does the Agency agree that the proposed approach is adequate to establish comparability between Mylan Insulin glargine manufactured in Malaysia and Mylan Insulin glargine manufactured in India?

c. Does the Agency agree that the physicochemical and biological studies comparing Mylan Insulin glargine manufactured in India with Lantus are adequate to support the approval

of the marketing application and that no additional studies are required comparing the product manufactured in Malaysia with reference product?

***FDA Response to Question 3:***

**a. See the response to 3 b below.**

**b. Your proposed comparability plan would be adequate provided that the comparability report in the NDA will include information on both process- and product-related impurities as well as on product-related substances and their biological activities. The information will need to be supported by comparative impurity profiles (e.g., chromatograms, retention times, and numerical results). Additional nonclinical and/or clinical studies may be required in support of any difference in the information. Provide stability data to compare your drug product manufactured in India and in Malaysia, including long term and accelerated storage conditions, stress conditions such as forced degradation and photostability, and in-use conditions.**

**Other comments:**

- **We remind you that the demonstration of comparability between the manufacturing sites in India and in Malaysia per ICH Guidance Q5E "Comparability of Biotechnological/Biological Products" would be acceptable provided that: these two sites are either your own facilities or your contract facilities and you have full access to all CMC information associated with both sites; this information will be submitted in your NDA (i.e., no Drug Master File will be submitted for either site); and the manufacturing processes at both sites starts with the same source material (i.e., working cell bank).**

- **Add a bioassay to the drug substance specification, and provide data to support the correlation of 0.036378 mg of insulin glargine being equal to 1 Unit of insulin glargine.**

- **If the differences between the manufacturing sites include any difference related to the pen injector, issues discussed in the response to questions 4 and 5 may be applicable.**

**c. Assuming that comparability is demonstrated between your product (drug substance and drug product) manufactured in India and in Malaysia, a demonstration of similarity between your product (drug substance and drug product) manufactured in Malaysia and US-approved Lantus and E.U.-approved insulin glargine would not be required provided that your similarity testing program for your product manufactured in India and US-approved Lantus and E.U.-approved insulin glargine will include the same analytical testing proposed for the product comparability exercises conducted for the product (drug substance and**

**drug product) manufactured in India and in Malaysia. In addition, provide stability data to compare the degradation profiles of your drug product manufactured in India and those of US-approved Lantus and E.U.-approved insulin glargine, including accelerated storage conditions, stress conditions such as forced degradation and photostability, and in-use conditions.**

**Additional Comment: For the combination product, manufacturing facilities are subject to 21 CFR Part 4.**

***Question 3 Discussion***: **The sponsor provided the following information to FDA's preliminary comments: Both facilities in India and Malaysia are Biocon facilities. No DMFs will be submitted in support of CMC site or manufacturing process, all CMC information will be submitted in the NDA. The working cell bank will be used at both sites. A bioassay based on USP<121> will be included in the drug substance specification. The detailed comparability protocol will be submitted to FDA for review. FDA acknowledged the sponsor's additional information and had no further comment.**

### 2.3 CDRH and CMC

***Question 4:*** Mylan intends to use its prefilled pen in the clinical studies to support that Mylan Insulin glargine and Lantus will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Comprehensive data on the prefilled pen will be provided in the IND submission.

Does the Agency agree that this information will be sufficient to support the use of the prefilled pen in the proposed clinical trials?

***FDA Response to Question 4:*** **We have the following comments regarding the data to be provided on the prefilled pen:**

- **Please provide a complete and detailed description of your proposed device.**
- **As several materials are used in the manufacture of the final pen injector, please provide a complete list of materials such as base materials, polymers, colorants, adhesives, inks, etc., used in the subject device and their Material Safety Data Sheets or Technical Data Sheets for evaluation.**
- **You have stated that you will provide test results from dose accuracy testing in accordance with ISO 11608-1:2012 to confirm the device delivers an accurate dose. However, in order to support the use of the pen in a clinical study the full performance assessment of the pen device should be provided. Please refer to and follow ISO 11608-1:2012, ISO 11608-2:2012 and ISO 11608-3:2012. Please perform all recommended tests and submit all test results to the Agency.**

- **The proposed biocompatibility tests are adequate to evaluate the pen component of injection system.**
- **It is unclear if the needle to be used with the pen is a 510(k) cleared device. If so, please provide the 510(k) number. Otherwise, please perform the biocompatibility tests according to ISO 10993-1 standard.**
- **The barrel of the pen injector appears to have ink markings. Under some circumstances residues derived from marking the device barrel can cause contamination of the drug. This contamination may affect the drug component or cause unintended exposure to for the patient. Please provide study report to show that the ink marking do not show any penetration into the drug compartment to cause contamination.**
- **The proposed in-use stability strategy is acceptable. Also, we remind you to include stability data in the NDA to show that the long-term storage under refrigerated conditions will have no adverse impact on the performance of the pen injector.**

- **Regarding the usability tests during development of the prefilled pen, please see addition comments in response to question #5**

***Question 4 Discussion*: The sponsor acknowledged the Agency's request to complete ISO 11608-1:2012, ISO 11608-2:2012, ISO 11608-3:2012 prior to initiation of the clinical trial with the pre-filled pen. The Agency reiterated that the strategy should follow standards listed in FDA's response (above).**

**Mylan confirmed that the needle used with the pen is a 510(k) device and that it will provide the 510(k) number to the IND. FDA asked the sponsor to confirm that the appropriate tests outlined in ISO 11608 (such as accuracy testing) include the proposed needle attached to the pen-injector to be marketed.**

**FDA noted the discussion of slide 8 shown by the sponsor at the meeting and Mylan provided the following explanation: the glass cartridge contains the drug and there is a gap in between the glass cartridge and cartridge holder; it is the cartridge holder that contains the ink markings, and there are no markings on the glass cartridge; due to the gap, studies for ink permeation or penetrations are not necessary. Mylan will notify the review division if there are changes to the described design made to the pre-filled pen (not changing the operating principles) after the clinical trials have been completed. Mylan asked whether the Agency would expect supportive clinical trials with this revised device beyond the human factor studies. FDA responded that, although this question focuses on the device constituent and not the clinical trials, it appears that Mylan plans to modify the device. FDA stated that sometimes even a minor change can affect the safety and effectiveness of the device, and any change to the device constituent part changes the combination product as a whole. Therefore, it is premature to**

**comment on the potential effects on the clinical trial program. If preliminary comments are sought, the sponsor should provide more details on the proposed modifications.**

**Finally, the sponsor asked the Agency to clarify what to evaluate for safety related to the device. FDA responded that in addition to items already broached in its written response to Question 4 (above), the sponsor should also perform accuracy testing after the device has been shipped, as well as shelf-life testing. FDA also asked the sponsor to include any observations/complaints by study subjects regarding device use.**

***Question 5:*** Mylan intends to conduct a summative human factors study in 120 users, using simulated use conditions in accordance with the Agency's advice provided in the Type C written response dated October 22, 2012 (Ref ID 3206476).

a. Does the Agency agree that the proposed summative human factors study design adequately supports approval of the NDA?

b. Mylan understands, from the scientific literature, that similar prefilled pens on the market are used by pediatric patients as well as adults. Mylan Insulin glargine injection is intended for administration in adults and children. Mylan will conduct the summative human factors study in adults (i.e. 18 years and above). Is this acceptable to the Agency as a basis of approval?

c. Mylan plans to conduct the proposed summative human factors study using one of its insulin analogues such that any differences in the IFU for device use with other insulin analogue candidates, such as the additional "mixing step" in insulin suspensions, are also validated. Since the summative human factors study for the prefilled pen is independent of the drug involved, is this approach acceptable to the Agency?

d. In the event that Mylan changes the color of the pen for aesthetic appeal alone, and makes no change to the functionality of the device, will the summative testing conducted with the current pen color still be acceptable for product approval?

***FDA Response to Question 5:***

**a. The general approach employed in your Human Factors/usability validation study appears adequate to support your proposed 505(b)(2) application in collecting the necessary data to demonstrate safe and effective use. However, there are some issues. As noted above in our response to Question 1, we are unable to comment on whether the design of these studies, in conjunction with other data, would provide adequate data to support a determination of therapeutic equivalence.**

- **We do not agree with your plan to have 50% of your participants use the insulin suspension in this study. All participants should use your proposed insulin glargine pen device for this study since the goal of this study is to demonstrated usability of your insulin glargine pen. We do not agree with**

**your plan to validate your Instruction For Use (IFU) for other insulin suspensions that involve an additional "mixing step." A separate human factors validation study needs to be conducted with the required number of participants for that particular insulin. If you want to include your insulin suspension prefilled pen in this study, you will need to double the number of participants so that each group of participant who will use the each type of insulin pen (i.e. insulin glargine and insulin suspension) has at least 15 participants.**

| Group | User | Insulin Type | Trained | Untrained | Total |
|---|---|---|---|---|---|
| 1 | Injection Naïve | glargine | N = 15 | N = 15 | N = 60 |
| | | suspension | N = 15 | N = 15 | |
| 2 | Injection Experienced | glargine | N = 15 | N = 15 | N = 60 |
| | | suspension | N = 15 | N = 15 | |
| 3 | Lantus Pen Users | glargine | N = 15 | N = 15 | N = 60 |
| | | suspension | N = 15 | N = 15 | |
| 4 | HCPs | glargine | N = 15 | N = 15 | N = 60 |
| | | suspension | N = 15 | N = 15 | |
| | Total | | N = 120 | N = 120 | N = 240 |

- **Additionally, you have not clearly described the use differences between the clear insulin and insulin suspension. We are unclear if the mixing step is the only difference, and what the mixing step entails in terms of different user interactions. Provide a comparison table that include all of the use steps for each insulin type and highlight the differences between the two IFUs. In addition, please describe the drug characteristics for the two insulin types, and clarify if those can impact user's ability to prepare and/or mix.**
- **We recommend conducting the pen identification task prior to the usability test of the device. Please provide a list of pens (insulin pens from other companies) and the rationale for inclusion in your pen identification task.**
- **Please refer to the comments provided in October 22, 2012, repeated here for your convenience: "Include a case-based protocol for differentiation between Biocon's pen and pens from other product lines likely to be prescribed with Biocon's pen, such as short- or rapid-acting insulin (e.g., insulin aspart, regular human insulin, etc.) as well as intermediate- and short-acting insulin combination products (e.g., NPH and regular human insulin combination or insulin aspart and insulin aspart protamine combination)."**
- **For the untrained group, we recommend that you do not specifically instruct participants to read the IFU prior to attempting to self inject. This will**

**simulate the actual use scenario regarding what users will do when training is not provided.**

**b. Regarding pediatric users, your table 1.6.1 shows the different populations:**

| Age | Recommendation |
|---|---|
| 6 years to 8 years | Administration by caregiver/ parent |
| 8 years to 12 years | Self-administration or administration by caregiver/ parent (as determined by caregiver/ prescribing physician). |
| 12 years to 18 years | Self-administration or administration under supervision of a caregiver/ parent. |
| 18 years onwards | Self-administration* |
| **A patient's ability to self-administer will be assessed by the prescribing physician. Geriatric patients may require assistance/ may be unable to self- administer insulin and/or insulin analogues.* | |

**You stated that self-administration or administration by caregiver/patient will be determined by caregiver/prescribing physicians for pediatrics between the age of 8 and 18 years old. This type of rationale makes it possible that some of these pediatric users may self-administer, and if that is the case, we expect to see 15 participants that are representative of this user group in your study. Alternatively, we ask that you specify the requirement that "no self-administrations should be performed by pediatric users under the age of 18 years old" in your product labeling and training.**

**c. Refer to our response to Question 5a.**

**d. Please ensure that the pens that you will evaluate in the summative study represent the finalized commercial product (i.e. pen color, including label and labeling). We recommend that you evaluate the appearance prior to validation. Alternatively, perform another differentiation study to ensure that the color change does not impact the user's ability to differentiate the pen from other products.**

**Additional comments:**

- **Include narrative and graphical description of your device, and describe the device user interface.**
- **Submit your human factors validation study protocol, finalized labeling including IFU, and analysis of use-related risks for review prior to implementation.**

***Question 5 Discussion:*** **No additional discussion.**

***Question 6:*** Mylan intends to follow the universal color code system initiated by the International Diabetes Federation (IDF), as a reminder aid so users can associate a color with its insulin formulation, where available. This is expected to reduce confusion and uncertainty between insulin and insulin analogues for users. If an IDF color is not available for a particular product, then the color will be similar to that used by the innovator, Sanofi.

Does the Agency agree with Mylan's approach to color-based differentiation between the same pen for different insulin analogues?

***FDA Response to Question 6:*** **Your plan appears acceptable. However, we will need to review the labels and labeling for each product to ensure that the differentiation scheme of your insulin pens is acceptable in conjunction with the differentiation study results.**

***Question 6 Discussion:*** **No additional discussion.**

### 2.4 Nonclinical

***Question 7:*** Glycosylated forms of insulin glargine are product-related variants generated during the manufacture of Mylan Insulin glargine drug substance. Through extensive characterization, Mylan has identified and elucidated the structures of each of the 5 glycosylated impurities. Additionally, as part of the qualification strategy, each of the impurities has been studied in several in-vitro/functional assays. A three-way, comparative, 28-day, repeat-dose toxicity study in Wistar rats has been successfully completed.

a. Does the Agency concur that the results from the three-way, 28-day repeat-dose toxicity study in rats predict the safety of glycosylated variants present at low levels in Mylan Insulin glargine?

b. Does the Agency agree that no additional nonclinical studies would be required to support approval of Mylan Insulin glargine?

***FDA Response to Question 7:***

**a. Based on your description provided in your briefing document, these impurities (glycosylated variants of drug substance; Basalog Batch G030008) appear to be addressed in your 3-way comparative 28-day bridging toxicity rat study (study No. G11066).**

**Please provide the level of these glycosylated variants in Lot BBS-0611003 used in the 90 day rat study (Study No. G4668) and 90 day rabbit study (Study No. G4669) as well as the 3-way comparative 28-day bridging rat toxicity study (study No. G11066). Please identify if the "Lantus" used in these 90-day toxicity studies is US-approved Lantus or EU-approved insulin glargine.**

**The adequacy of non-clinical studies will be determined during review of your NDA submission along with the CMC determination of adequacy of your impurities characterization. If there is any new concern identified by CMC, additional nonclinical studies may be required to assess these impurities and concerns.**

**b. See response to Question 7a and 8, as you may need a nonclinical study to bridge between proposed manufacturing sites.**

***Question 7 Discussion:*** **No additional discussion.**

### 2.5 Clinical

***Question 8:*** Mylan plans to rely on the Agency's finding of safety and efficacy for the reference drug, Lantus (NDA 21081). Mylan plans to use Lantus sourced from the EU and Lantus sourced from US as comparators in the proposed clinical development program. A scientific bridge between Lantus sourced from the US, and Lantus sourced from the EU has been established.

Does the Agency agree that, the proposed three-way comparative development program and data generated to date for Mylan Insulin glargine, Lantus sourced from the US, and Lantus sourced from the EU is adequate to establish a scientific bridge?

***FDA Response to Question 8:*** **As a preliminary matter, FDA notes that E.U.-approved Lantus is not an approved product in the United States. Accordingly, it is not a "listed drug" for which FDA has made a finding of safety and effectiveness.[1] The 505(b)(2) approval pathway may be used for a product that is demonstrated to be sufficiently similar to a listed drug (i.e., U.S.-approved Lantus) to permit reliance, where scientifically justified, on FDA's finding of safety and/or effectiveness for the listed drug to support the approval of a new drug application. See FDA's previous regulatory comments regarding the 505(b)(2) pathway.**

**If Mylan seeks to use data from a clinical trial comparing Mylan insulin glargine to E.U.-approved insulin glargine to support a demonstration of sufficient similarity to the U.S.-approved listed drug and thereby justify reliance, in part, on FDA's finding of safety and effectiveness for the listed drug, Mylan should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of similarity and establish an acceptable scientific bridge to the U.S.-approved listed drug. The type of bridging data needed to provide adequate scientific justification for this approach would include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., Mylan Insulin glargine, US-approved Lantus, and EU-approved insulin glargine) and bridging clinical PK and PD study data for all three products. All three pairwise comparisons should meet the pre-specified acceptance criteria for analytical and PK and PD similarity. The adequacy of this scientific justification and bridge to the U.S.-approved listed drug would be a review issue.**

[1] We note that your submission uses the term "reference product." The term "reference product" means the single biological product licensed under section 351(a) of the PHS Act (see section 351(i)(4) and 351(k) of the PHS Act). There currently is no "reference product" licensed under section 351(a) of the PHS Act for a proposed insulin glargine product. Since you intend to use the 505(b)(2) approval pathway, in this response we use the term "listed drug" to refer to US-approved Lantus.

**While a 3-way comparative bridging 28-day rat toxicity study has been performed with both US-approved Lantus and EU-approved insulin glargine, the levels of impurities have not been provided (See response to Question 7a).**

**You plan to utilize two manufacturing sites for your proposed product and demonstrate comparability of products from these sites using primarily analytic/chemical means. This type of CMC data is required for the NDA filing. If you plan to utilize products from both sites in your Phase 3 clinical program, then adequate safety data will be needed to show comparability of safety prior to clinical use. Therefore additional nonclinical safety data (e.g. subchronic toxicity) will likely be needed (See response to Question 7A).**

**See the response to Question 3 c regarding the chemistry requirements.**

**Based on the results reported in the briefing book, it appears that a clinical PK and PD bridge has been established between US-approved Lantus and EU-approved insulin glargine. However, the determination of the adequacy of clinical PK and PD bridge will be a review issue.**

***Question 8 Discussion:*** **The sponsor clarified that it plans to use EU-approved insulin glargine as an active control in its Phase 3 study for type 1 diabetes mellitus and US-approved Lantus as an active control in its Phase 3 study for type 2 diabetes mellitus. FDA acknowledged the clarification, and recommended that a single product (i.e., EU-approved insulin glargine or US-approved Lantus) be used as an active control, rather than using two distinct products (i.e., EU-approved insulin glargine and US-approved Lantus) in a single clinical study.**

**FDA clarified the use of two different methods (Mercodia and Dako) for sample analysis from bioequivalence studies. Sponsor stated that backup samples from Study GLARGCT100111 were reanalyzed using a more sensitive assay following FDA advice from previous interactions.**

***Post-Meeting FDA Comment to Question 8: In your submission, in addition to reporting the serum M2 values from the new assay, also report the C-Peptide values at baseline and for the duration of clamp. Also include the relevant bioanalytical method reports for insulin, C-peptide, and glucose analytes.***

***Question 9:*** Mylan plans to conduct two supportive clinical studies. Mylan intends to conduct a 52-week comparative study in T1DM patients with approximately 400 patients using EU sourced reference product. The planned T1DM study will have a 6-week run-in period followed by a 52-week treatment period and finally an additional 4-week of follow-up. In addition, Mylan intends to conduct a 24-week comparative clinical study to evaluate safety, immunogenicity, and efficacy in T2DM patients with at least 500 patients using EU sourced reference product. The T2DM study will have a 6-week run-in period followed by a 24-week treatment period and a 4 week follow-up.

a. Does the Agency agree that the proposed T1DM and T2DM studies have the appropriate design, sample size and endpoints to support approval?
b. Given that Mylan will provide a scientific bridge between the Lantus US and Lantus EU, does the Agency agree that the use of Lantus sourced from the EU in the proposed T1DM and T2DM studies has no impact on its role in supporting a TE determination?
c. Does the Agency agree with Mylan's plan to include 6 month data from the T1DM study for the initial NDA submission and to submit the 12 month data as an amendment to the NDA or as a post approval commitment?

***FDA Response to Question 9:***

**a. See our response to Question 1. Based on the synopsis provided in your briefing document, we have the following preliminary comments for the proposed T1DM (MYL-GAI-3001) and T2DM (MYL-GAI-3002) studies. We strongly recommend that you submit the full study protocols along with any statistical analysis plan for our review and await our comments before commencing your Phase 3 studies. The protocol should also include how you will evaluate safety related to device.**

- **Your proposed sample size of 200 patients per arm for Study MYL-GAI-3001 is insufficient to assess important safety events. Increase the sample size per treatment arm to at least 250 subjects to ensure that there will be a sufficient safety database.**

- **Clarify the sample size for Study MYL-GAI-3002. The synopsis stated 560 subjects, whereas the main body of the briefing document stated 500 subjects will participate in this study.**

- **We note that T2DM patients already on Lantus are eligible for enrollment in Study MYL-GAI-3002. In order to facilitate detection of anti-insulin antibodies and their titers in the two treatment arms, we also recommend that you enroll T2DM subjects who are naïve of insulin treatment for participation in the study. The randomization can be stratified by prior insulin use (yes or no) and you should analyze antibody response separately for insulin-naïve and non-insulin-naïve subjects.**

- **We note that in the HbA1c inclusion criterion is <8.5% for Study MYL-GAI-3002. To ensure that there will be opportunity to sufficiently titrate insulins and more convincingly show non-inferiority, you should enroll patients with sufficiently high baseline HbA1c (e.g., mean baseline HbA1c ~8.5%).**

- **We agree with the non-inferiority margin proposed. However, iInsulin is a product that is titrated to achieve a targeted glycemic effect. Therefore, the risk/benefit profile for your insulin glargine (compared to Lantus) will also be based on other important effects, such as rates of hypoglycemia, changes in body weight, and other safety issues that emerge during the NDA review.**

- **Adequate titration of insulins will be a critical factor in determining a meaningful improvement in HbA1c over the duration of the study and the interpretability of study results. Therefore, we recommend strategies to ensure that appropriate titration of insulin doses occur, such as a titration algorithm, and/or review of glucose data while the trials are ongoing with feedback to investigators when there is evidence of inadequate titration. You should consider a titration algorithm that takes into account fasting plasma glucose level so that most titration occurs by Weeks 6-12. If insulin doses are not relatively stable after Week 12, interpretation of study results could be affected because HbA1c at Week 24 will not accurately reflect glycemic control.**

- **We ask that you clarify which are key secondary endpoints and how you will control for Type 1 error in the study protocol.**

- **You propose 'rate of hypoglycemic events per 30 days at 4 weeks and 24 weeks' as one of secondary endpoints. Evaluation of hypoglycemia should be based on the entire treatment intervention phase (i.e., titration and maintenance phase). Titration and maintenance phases provide relevant clinical information that should be captured in the analysis.**

- **Your trial is open-label and reporting bias is possible for episodes of hypoglycemia that rely on fingerstick glucose measurements alone without clinical symptoms.**

- **The dropout rate, 2%, for Study MYL-GAI-3002 seems low and unrealistic. You may want to adjust sample size with a higher anticipated dropout rate.**

**b. Your question regarding the acceptability of use of EU-approved insulin glargine in clinical studies intended to support a demonstration of therapeutic equivalence of Mylan insulin glargine to U.S.-approved Lantus requires further internal Agency discussion and we are unable to provide a response at this time.**

**c. We recommend that your NDA should be complete at the time of submission, as the 12 month data from this study are important in determining the safety of your drug in this population.**

***Question 9 Discussion:*** **The sponsor asked the Agency to clarify what to evaluate for safety related to the device. FDA provided the following clarification: The overall safety profile for the combination product includes the device constituent; Examples of device related adverse events and device malfunctions include, but are not limited to, local skin reactions, wet injections, needle breakage, failure to inject, etc. FDA stated that it would be useful to provide details on the method / patient collection tool to capture details on the device related events in the protocol. The Agency can provide additional comments during protocol review.**

**The sponsor stated that the key secondary endpoints are safety-related and do not plan to control for Type 1 error. FDA agreed that control for Type 1 error is not necessary for safety-related key secondary endpoints, but will be needed for any efficacy-related key secondary endpoints.**

**The sponsor provided information on titration guidelines for its Phase 3 studies. FDA reiterated that adequate titration of insulins will be a critical factor during the review process and recommended having a titration committee to review glucose data while the trials are ongoing to make sure that there is adequate insulin titration, and the sponsor stated that they will take that into consideration.**

**The sponsor clarified that the sample size for Study MYL-GAI-3002 is 560 subjects (not 500 subjects). The sponsor will enroll insulin-naïve subjects in their T2DM study as suggested by the Agency, but did not have a specific ratio for enrollment of insulin naïve subjects. FDA stated that there should be a ratio to make sure that sufficient number of insulin-naïve subjects are enrolled into the study, and will recommend a ratio to the sponsor after the meeting.**

**Mylan asked whether the use of EU-approved insulin glargine as an active control in a clinical study intended to support a demonstration of therapeutic equivalence of Mylan insulin glargine to U.S.-approved Lantus would pose an additional hurdle if they provided adequate bridging data. FDA reiterated that Mylan's question requires further internal Agency discussion and they were unable to provide a response at this time, but noted that this would be an additional factor to consider. FDA noted that if Mylan was proposing a clinical study to support a demonstration of therapeutic equivalence, the sponsor could submit a proposal for such a study with rationale for their study objectives and design, and the Agency may review their proposal and provide comments**.

***Post-Meeting FDA Comment to Question 9: We recommend that 40-60% of total subjects enrolled in Study MYL-GAI-3002 are T2DM subjects who are naïve of insulin treatment.***

***Question 10:*** Mylan plans to execute the T1DM and T2DM clinical studies using prefilled pens. No additional studies are planned using vials. The formulation for all presentations of Mylan

Insulin glargine is the same. We anticipate that the T1DM and T2DM studies done with the prefilled pen will be sufficient for the approval of the vial also.

Does the Agency agree that no further clinical studies are required using vials to support approval of the vial presentation?

***FDA Response to Question 10:*** **We agree that additional clinical studies using vials are not necessary for approval of the vial presentation if the clinical properties of your insulin glargine are expected to be the same for all presentations. Refer to comments from other FDA disciplines (Pharmacology/Toxicology, CMC, and Clinical Pharmacology) on the other aspects of your proposal.**

***Question 10 Discussion:*** **No additional discussion. Mylan withdrew their new question on slide 20.**

***Post-Meeting FDA Comments to Question 10: Our previous response is contingent upon studies on leachables and extractables from the vials. If these studies show that the impurities from the vials are different from the prefilled pens, you may need additional data or clinical studies (e.g., immunogenicity data) to support approval of the vial presentation.***

***Question 11:*** Patients recruited for T1DM study will have at least 3 months history of exposure to a stable dose of Lantus. The pre-exposure to Lantus is intended to reduce differences in baseline immunogenicity between the two treatment arms. We will be collecting blood samples for the immunogenicity assessment at screening, baseline, and weeks 12, 24, 36 and 52. We are planning on conducting an interim analysis after the patients complete 24 weeks of treatment and submit the clinical study report to Europe for marketing authorization approval. Thus the immunogenicity analysis will be conducted at 2 time points during this 52-week study at 24 weeks and at 52 weeks.

a. Is the proposed immunogenicity sampling at screening, baseline, and weeks 12, 24, 36 and 52 acceptable?

b. Mylan is planning to conduct immunogenicity analysis for all the patients at 2 time points; an interim analysis at 24 weeks and a final analysis at 52 weeks. Is the proposed analysis plan acceptable?

***FDA Response to Question 11:*** **See our response to Question 9c. We recommend that you submit the final analysis with 52 weeks data at the time of NDA submission.**

**The proposed immunogenicity sampling is acceptable to support your proposed 505(b)(2) application . The immunogenicity analysis should include the effect of treatment on anti-insulin antibody development, and also correlate these antibodies with glycemic response (i.e., HbA1c), hypoglycemia, allergic reactions, and emerging safety issues. As noted above in our response to Question 1, we are unable to comment**

**on whether the design of these studies, in conjunction with other data, would provide adequate data to support a determination of therapeutic equivalence.**

***Question 11 Discussion:*** **The sponsor asked whether 9 month data from the T1DM study is sufficient for NDA filing, with the full 12 month data to be submitted during regulatory review. FDA recommended that the sponsor file the NDA with 12 month data from its T1DM study.**

**FDA stated that interim data analysis should be included in their statistical analysis plan.**

***Post-Meeting FDA Comments to Question 11a: We also ask that you obtain samples for immunogenicity analysis at 10-15 days and 28-35 days after randomization.***

***Question 12:*** The presentations of the test product and the comparator planned to be used for clinical studies are clearly distinguishable (different prefilled pens). We are unable to double mask the studies and the double dummy design technique is not ethical or feasible, therefore, the proposed studies will be open label. However, we plan to conduct the efficacy parameter (HbA1C) and safety parameters (Biochemical laboratory tests) in a blinded manner. This approach diminishes potential bias that would otherwise exist from an open-label, trial design as these are objective parameters.

Does the Agency agree with the open label design for the proposed clinical studies?

***FDA Response to Question 12:*** **The open label design is acceptable given that you are using prefilled pens in these clinical studies.**

***Question 12 Discussion:*** **No additional discussion.**

***Question 13:*** Mylan plans to perform the clinical trials with Lantus and Mylan Insulin glargine using prefilled pens. EU guidance requires that the retained samples be stored in the EU. FDA guidance does not explicitly state where the testing samples should be stored. Mylan plans to store samples, equivalent to two times the amount needed for full analytical testing from all batches used in the clinical trials of test and reference product, in the EU.

Does the Agency agree with Mylan's proposal to store two times the amount needed for full analytical testing of batches used in clinical trials (both test and reference product) in the EU?

***FDA Response to Question 13:*** **Yes, we agree that the reserved sample should be at least twice the quantity necessary for all analytical testing.**

***Question 13 Discussion:*** **No additional discussion.**

***Question 14:*** Mylan is plans to execute a clinical study in T1DM patients. T1DM patients are typically treated with Insulin/Insulin Analogs per standard of care. It is practically impossible to

obtain serum from insulin treatment naïve T1DM patients. In addition our T1DM study is designed to only include patients that have at least a 3-months history of exposure to a stable dose of Lantus. For these reasons Mylan would like to propose to use pre-dose sera from the T1DM study patients to establish cut-points using the balanced design.

Does the Agency agree with Mylan's approach to use pre-dose patient sera to establish screening and confirmatory cut-points during immunogenicity method validation?

***FDA Response to Question 14:*** **Response to Question 14 will be provided in the final Meeting Minutes as Post-Meeting Comments.**

***Question 14 Discussion:*** **Yes, in this population this is acceptable provided samples that are confirmed to have anti-drug antibodies are not used for the determination of the assay cut point.**

***Post-Meeting FDA Comments to Question 14: See Discussion above; no additional post-meeting comments.***

***Question 15:*** The T1DM study has been designed to compare the immune responses between Mylan Insulin glargine and Lantus. Any differences in immune responses between the treatment arms could be assessed with the currently planned analytical methods. The additional analysis of anti-drug antibody (ADA) positive samples for cross-reactivity to insulin or related analogues would have no impact on the outcome of the trial. In case the characterization of cross-reacting ADA is required Mylan plans an additional Comprehensive Confirmatory Analysis phase where the confirmed positive samples undergo pre-incubation with an excess unlabeled human insulin and insulin lispro prior to adding Lantus or Mylan Insulin glargine. The difference in percent inhibition between Mylan Insulin glargine and Lantus will be determined.

a. Does the Agency agree that an analysis of anti-drug antibody positive samples for cross-reactivity to insulin or related analogues is not required for the immunogenicity assessment of the clinical studies?

b. In case the analysis of cross-reacting ADA is required does the Agency agree with Mylan's approach of using excess unlabelled human insulin and insulin lispro to analyse confirmed positive samples?

***FDA Response to Question 15:*** **Response to Question 15a and 15b will be provided in the final Meeting Minutes as Post-Meeting Comments.**

***Question 15 Discussion:*** **No, the Agency does not agree that an analysis of anti-drug antibody positive samples for crossreactivity is unnecessary. In general, the approach of adding excess unlabeled human insulin to assess crossreactivity is adequate, but a final determination will be made upon review of the assay.**

***Post-Meeting FDA Comments to Question 15: See Discussion above; no additional post-meeting comments.***

***Question 16:*** During method development, Mylan plans to compare the Radio Immuno-precipitation and the Meso-scale Discovery assay format in terms of method validation parameters including intra and inter assay precision for screening, confirmatory and titration assays, sensitivity, selectivity, specificity and free drug tolerance. Based on the data obtained from the comparison, Mylan intends to select one assay format for validation and sample analysis.

Does the Agency agree with Mylan's approach of comparing both radioactive and non-radioactive assay formats, and selecting a single format for validation and sample analysis?

***FDA Response to Question 16:*** **Response to Question 16 will be provided in the final Meeting Minutes as Post-Meeting Comments.**

***Question 16 Discussion:*** **The Agency has no preference for assay format. The Sponsor will need to select an assay format and validate its performance prior to testing the samples of the pivotal trials. A final determination will be made upon review of the SOP and validation of the assay used.**

***Post-Meeting FDA Comments to Question 16: See Discussion above; no additional post-meeting comments.***

***Question 17:*** Mylan is planning to use two separate immunogenicity assays using an identical analytical platform (RIPA or MSD), one for Mylan Insulin glargine and one for Lantus. A blinded anti-drug antibody analysis would require all samples being analyzed in both assays resulting in two data sets for each sample. Mylan intends to un-blind the study samples at the CRO before initiation of sample analysis.

Does the Agency agree with Mylan's approach of un-blinding the immuno-genicity samples before initiation of the sample analysis?

***FDA Response to Question 17:*** **Response to Question 17 will be provided in the final Meeting Minutes as Post-Meeting Comments.**

***Question 17 Discussion:*** **The advantages of having a single platform for testing the samples for antibodies to Mylan and Lantus product were discussed. The Agency does not agree that unblinding the samples is necessary prior to testing them. The sponsor requested that additional discussion be held regarding this topic between the Sponsor and the Agency.**

***Post-Meeting FDA Comments to Question 17: See Discussion above; no additional post-meeting comments.***

***Question 18:*** Does the Agency agree with Mylan's approach of using a competitive ligand binding Assay format for the evaluation of neutralizing antibodies?

***FDA Response to Question 18:*** **Response to Question 18 will be provided in the final Meeting Minutes as Post-Meeting Comments.**

***Question 18 Discussion:*** **This question was not discussed during the meeting but the Sponsor requested a comment.**

***Post-Meeting FDA Comments to Question 18: The approaches described to assess neutralizing activity of samples that test positive for antibodies to the product is adequate, but a final determination will be made upon review of the SOP and validation of the assay.***

**Additional FDA Comment:**
**FDA recommends that you submit your proposed proprietary name for this product for review. (See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf**

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/s/

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JEAN-MARC P GUETTIER
04/04/2014