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APPLICATION NUMBER:

210605Orig1s000

OTHER ACTION LETTERS



NDA 210605

COMPLETE RESPONSE

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, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for insulin glargine injection 100 units/mL.

We acknowledge receipt of your amendment dated February 28, 2019, which constituted a complete response to our May 17, 2018, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS MAJOR DEFICIENCIES

During a recent inspection of Biocon Sdn. Bhd. FEI#3011248248, a manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

We note that this is the second Complete Response letter for this NDA that has identified inspectional observations at this manufacturing facility as a deficiency. We recommend that you work with this manufacturing facility for your insulin glargine product and apply the necessary resources to address these inspectional observations in a timely manner.

PRESCRIBING INFORMATION

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR

Requirements for Prescribing Information¹ and Pregnancy and Lactation Labeling Final Rule² 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 in the PI on 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.

During our review of your submitted labeling, we identified the following labeling issues that should be addressed in your resubmission:

In the Instructions for Use (IFU) labeling for the pen injector presentations submitted on August 28, 2019, you added the word "Needle" to the Step 8 title as follows "Step 8 Needle disposal." Please update the language in other places of the IFU that reference step 8. For example, the required supplies section states (b) (4) at the end of these Instructions for Use". Please revise to "See Step 8 Needle disposal" in all such instances where it is appropriate to do so.

In addition, the pen IFUs use (b) (4) to indicate sub-bullets under each step (i.e., Step 1, Step 2, etc.). Please note that we consider this to be a major change to the IFU, which was validated by the Human Factors study. Therefore, please revert to the prior sub-bullet letter designations (A, B, C, etc.) under each numbered step that were used in the Human Factors study.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

¹ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

² <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling that is identical to the carton and container labels submitted on August 28, 2019.

PROPRIETARY NAME

Please refer to correspondence dated May 1, 2019, which addresses the proposed proprietary name, Semglee. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. Furthermore, as explained in FDA's final guidance on *Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009*,⁴ "an original 505(b)(2) application (including a resubmission) for a biological product that relies, at least in part, on FDA's finding of safety and/or effectiveness for a listed drug that is a biological product will receive a complete response if the application is pending at the end of the day (11:59 pm Eastern Daylight Time (EDT)) on Friday, March 20, 2020, because the NDA for the listed drug relied upon will no longer exist at midnight on Monday, March 23, 2020."

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

⁴ Available at <https://www.fda.gov/media/119590/download>

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.⁵

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Deputy Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

⁵ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
08/28/2019 02:50:21 PM



NDA 210605

COMPLETE RESPONSE

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, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for insulin glargine injection 100 units/mL.

We also acknowledge receipt of your amendment dated May 11, 2018, pertaining to antimicrobial effectiveness testing, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL-RELATED MAJOR DEFICIENCIES

1. Your 505(b)(2) application requests approval of your proposed insulin glargine product manufactured using Process VI at a facility in Malaysia (i.e., Process VI product), while the proposed 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.

2. You have not submitted the bridging data necessary for approval of the vial presentation of your proposed product. The recommendation regarding the need for PK/PD data between your cartridge and vial presentations was also conveyed during the Type A, Informal Conference held on August 15, 2017. Submit the results from the proposed study (Study MYL-1501D-1004) to address this deficiency.

PRODUCT QUALITY-RELATED MAJOR DEFICIENCIES

3. During a recent inspection of Biocon Sdn. Bhd. FEI#3011248248, a manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.
4. CMC microbiology review noted the following deficiencies:
 - i. Lack of method suitability data for endotoxin, sterility, and antimicrobial effectiveness testing (AET).
 - ii. Lack of AET data supporting the product expiry from stability.

To resolve these deficiencies, provide the following in your resubmission.

- a) Provide AET results for the 10 mL drug product presentation, which contains polysorbate 20, (b) (4) at or below the minimum content specification for release or stability testing (whichever is lower). Also, provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch per drug product presentation (i.e. one 3 mL cartridge drug product presentation and one 10 mL vial drug product presentation) at the end of the proposed shelf life. Refer to ICH Q1A Stability Testing of New Drug Substances and Products for new drug products.
- b) It is stated in your March 19, 2018 response that bacterial endotoxins testing method suitability was performed for the 10 mL drug product presentation including polysorbate 20 and the 3 mL cartridge drug product presentation. However, only brief summaries were provided. Provide the reports showing the actual results for the bacterial endotoxins method suitability studies.

It is stated in your March 19, 2018 response that sterility testing method suitability was performed for the 10 mL drug product presentation including polysorbate 20 and the 3 mL cartridge drug product presentation. However, only brief summaries were provided. Provide the reports showing the actual results for the sterility method suitability studies.

HUMAN FACTORS-RELATED MAJOR DEFICIENCIES

5. Our review determined that there were an insufficient number of untrained injection naïve pediatric patients in each user group of the human factors validation study. Our review of the Instructions for Use (IFU) identified several areas that should be modified from a medication error perspective (see **INSTRUCTIONS FOR USE** below). You may also consider additional labeling changes as necessary. Once you finalize your proposed to-be-marketed IFU, you should conduct an additional human factors validation study with 15 untrained injection naïve pediatric patients.
6. We note that the results of product differentiation showed multiple study participants failed to select the Semglee pen. Our review of the proposed carton and container labeling (see **CARTON AND CONTAINER LABELING** below) identified multiple areas that should be modified to enhance product differentiation. Therefore, you should implement these modifications, in addition to any other labeling changes that you consider to be necessary, finalize your proposed to-be-marketed carton and container labeling, and conduct a differentiation study with all the intended user populations for the product with at least 15 users in each distinct user group.

We recommend that you submit the protocols for the usability study and differentiation study for Agency review and feedback prior to starting your studies.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). 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 in the PI on pregnancy, lactation, and females and males of reproductive potential;
- Regulations and related guidance documents;
- A sample tool illustrating the format for Highlights and Contents;
- 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.

During our review of your submitted proposed labeling, we identified the following labeling issues that should be addressed in your resubmission:

1. Dosage and Administration: Section 2.1 Important Administration Instructions
 - a. We recommend replacing the word (b) (4) in the statement “administer Semglee subcutaneously into the abdominal area, thigh, or (b) (4) ...” to “upper arm” as this corresponds to the instructions provided in the Instructions for Use (IFU). In addition, we recommend adding “buttocks” as an administration site to align with the information provided in the IFU.
 - b. We recommend adding the statement “Use the Semglee prefilled pen with caution in patients with visual impairment.” as the final bullet in this section.
2. Dosage and Administration: Section 2.2 General Dosing Instructions
 - a. We recommend adding the statement “Semglee prefilled pens are designed to dial doses in 1 unit increments” as the final bullet in this section.
3. Dosage and Administration: Section 2.4 Changing to Semglee from Other Insulin Therapies
 - a. We do not agree with removing the statement (b) (4). Therefore, we recommend adding the following statement as a new bullet this section: “In patients changing from once daily NPH insulin to once daily dose of Semglee, the recommended initial Semglee dose is the same as the dose of NPH that is being discontinued.”
4. How Supplied/Storage and Handling: Section 16.1 How Supplied
 - a. We recommend reformatting this section using the following table to present this information.

Semglee	Total Volume	Concentration	Total Units Available in Presentation	Dose Increment	NDC Number	Package Size
U-100 vial	10 mL	100 units/mL	1,000 units	n/a	(b) (4)	1 vial
U-100 prefilled pen	3 mL	100 units/mL	300 units	1 unit		1 pen
						3 pens
						5 pens

5. How Supplied/Storage and Handling: Section 16.2 Storage
 - a. We recommend revising the temperature presentations in the table to present the Fahrenheit temperatures before the Celsius temperatures as this coincides with the temperature presentation in the IFU. In addition, Fahrenheit temperature is more likely to be understood by end users in the US.

Prior to resubmitting the proposed labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

We reserve additional comments on the proposed labeling until the application is otherwise adequate.

INSTRUCTIONS FOR USE

Submit draft Instructions for Use (IFU)-Pen labeling revised as follows:

1. We recommend that you revise the statement (b) (4) (b) (4) to read as follows for improved clarity: “Semglee is a prefilled disposable pen injector that contains a total of 300 units of insulin glargine. One pen contains multiple doses of medicine. You can select doses from 1 to 80 units in steps of 1 unit.” In addition, we recommend adding the statement “If your prescribed dose is more than 80 units, you will need to give yourself more than 1 injection.” to this paragraph.
2. We recommend that you move the statement “**Do not** leave the needle attached to the Pen during storage or reuse needles.” so that it is immediately following the statement “Always store the Pen with the cap on, to prevent contamination.”: “Always store the Pen with the cap on, to prevent contamination. **Do not** leave the needle attached to the Pen during storage or reuse needles.”
3. Due to the use errors involving the storage of Semglee observed in the HF study, we provide the following recommendations for the storage information. Under the Storage heading, we recommend adding section subheadings and bullet points to increase clarity and readability of the statements. In addition, we recommend modifications to the language as follows:

Storage **Unused Pens**

- Before using the Pen, store the cartons containing the Pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Unused Pens may be used until the expiration date printed on the carton, if

the Pen has been kept in the refrigerator.

- Do not freeze the Pen.

In-use Pen

- Before first use, take a Pen out of the refrigerator, rest it on a flat surface, and wait for it to reach room temperature between 59°F to 86°F (15°C to 30°C).
- While using the Pen, store it at room temperature up to 86°F (30°C). Do not put the Pen back in the refrigerator after using it.
- Always store the Pen with the cap on, to prevent contamination. Do not leave the needle attached to the Pen during storage or reuse needles.
- The Pen that you are using should be thrown away 28 days after the first use, even if the Pen has insulin left in it. See disposal instructions in Step 8.

Keep your Pen and needles out of sight and reach of children.

Always use a new sterile needle for each injection as this helps stop blocked needles and prevents infections.

4. Step 4: Select your dose

- a. We recommend the addition of the following as bullet points under this heading: “-The Pen dials 1 unit at a time.”, “-The Dose Knob clicks as you turn it.”, “-**Do not** dial your dose by counting the clicks because you may dial the wrong dose.”, “-The **even** numbers are printed on the dial. The odd numbers are shown as lines.”
- b. We recommend the addition of an image of an odd dose dialed on the device pen to correspond with the language added to indicate that odd doses are shown as lines in the dose window.
- c. We recommend that you add the statement “If you need a dose greater than 80 units, you should give it as two or more injections.” so that it immediately follows the statement “**Do not** force the dose knob to turn beyond 80 units.”: “**Do not** force the dose knob to turn beyond 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.” In addition, we recommend that these statements are moved to immediately follow the statement “The dose can be corrected by turning the dose knob in either direction until the correct dose lines up with the yellow dose pointer.” to increase prominence of this information in the IFU.

5. Step 5: Select and clean the injection site

We recommend revising the statement “Select the injection site as explained...” to read as follows:

“Select the injection site as explained to you by your healthcare provider. Semglee is injected under the skin (subcutaneously) of your arms, hips, thighs, buttocks, or

abdomen. You should change your injection site for each injection. Clean with a new alcohol wipe and let your skin dry before you inject your dose.”

6. Due to the use errors with holding the dose button down to complete the injection observed in the HF study, we provide the following recommendation for Step 6: Inject your dose:

Under step D, revise the statement “hold the purple injection button...is injected.” as follows for improved clarity: “after the dose window shows “0”, continue to hold the purple injection button down and slowly count to 10 to make sure that the full dose of insulin is injected.”

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

A. Container Label-Pen

1. The proposed proprietary name, “Semglee,” the established name, and the product strength lack prominence on the container label and are not readable. Thus, we request that you revise the label to remove the (b) (4) (b) (4) interfering with the readability of this information on the label in accordance with 21 CFR 201.10 (a) and 21 CFR 201.15 (a)(6). Consider presenting this text (proprietary name, established name, and product strength) on a white background with black letters in larger font to improve readability.
2. To improve readability of the proprietary name, we recommend increasing the font size of “Semglee” on the label.
3. To improve readability of the product NDC, we recommend using black font on a white background.
4. To improve the readability of the “Rx only” statement, we recommend removing the (b) (4) and using black font.
5. Increase the font of the “For Single Patient Use Only” statement to improve readability of this information.

B. Container Label-Vial

6. The product strength, 100 units/mL (U-100), is illegible and difficult to read due to the use of the (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability.

7. To improve the readability of the “Rx only” statement, we recommend removing the (b) (4) and using black font.

C. Carton Labeling-Pen

8. The product strength, 100 units/mL (U-100), is illegible and difficult to read on each of the carton presentations due to your use of the (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability. In addition, move the product strength statement so that it is directly below the proprietary name and established name on the principle display panel.
9. To improve the readability of the “Rx only” statement, we recommend removing the (b) (4) and using black font.
10. We recommend that you consider moving the statement (b) (4) from the PDP so that it is immediately above (b) (4) on the back panel. In addition, for improved clarity of the statement, we recommend that you modify the statement to read “Use each pen within 28 days after initial use.”

D. Carton Labeling-Vial

11. The product strength is illegible and difficult to read on each of the carton presentations due to your use of the (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability.
12. To improve the readability of the “Rx only” statement, we recommend removing the (b) (4) and using black font.
13. To improve readability of the carton contents, we recommend moving the statement “One 10 mL vial” above the blue box area and changing “one” to black font.

PROPRIETARY NAME

Please refer to correspondence dated, November 14, 2017, which addresses the proposed proprietary name, Semglee. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

PRODUCT QUALITY

- 1) Revise the methods used for the determination of high molecular weight proteins (HMWP) and Product related substances to include the following:
 - i. Equations used for impurity calculations to the HPLC and SEC impurity methods.
 - ii. HPLC peak resolution criteria of not less than 2.0 for impurities to the system suitability
- 2) Provide the following additional information for aged drug product:
 - i. Individual impurity profile comparison for MYL-1501 D drug product at the end of expiration (24 (b) (4) months) and in-use period using USP and in-house insulin glargine methods.
 - ii. Individual impurity profile comparison for MYL1501 D drug product (cartridges and vial) with the available stability data of Lantus at T24 and T36 month time points using in-house impurity method.
 - iii. Side by side accelerated stability impurity profile information for age matched Lantus and MYL-1501D vial and cartridge batches.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

WILLIAM H CHONG
05/17/2018