

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125469Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA #                      BLA125469  
Product Name:                TRULICITY (dulaglutide)

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PMR/PMC Description:      A 26-week randomized, double-blind, placebo controlled study of the safety, efficacy, and pharmacokinetics (PK) of Trulicity (dulaglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive) with or without concomitant metformin therapy, followed by a 26-week open-label extension. As part of this study, sparse blood samples for population PK and exposures-response analysis will be collected. This trial should not be initiated until after the data from the juvenile toxicity study have been submitted to and reviewed by the Agency.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>February 2016</u>
	Study/Trial Completion:	<u>August 2022</u>
	Final Report Submission:	<u>January 2023</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Dulaglutide is ready for approval for use in adults. However, pediatric studies had been deferred until adequate safety data was available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is a deferred pediatric study under the Pediatric Research Equity Act (PREA) to assess the pharmacokinetics, efficacy and safety of dulaglutide in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 26-week randomized, double-blind, placebo controlled study of the safety, efficacy, and pharmacokinetics of TRULICITY (dulaglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive) with or without concomitant metformin therapy, followed by a 26-week open-label extension. As part of this study, sparse blood samples for population PK and exposures-response analysis will be collected. At least 30% of randomized patients should be 10 to 14 years of age, and at least one-third (but not more than two-thirds) of patients in both age subsets should be female. This trial should not be initiated until after the data from the juvenile toxicity study have been submitted to and reviewed by the Agency.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

**Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

**Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Dulaglutide juvenile toxicity study with direct dosing of immature rats (postnatal day 7) to assess potential effects on sexual maturation, reproduction and CNS development and function.

Required

- Observational pharmacoepidemiologic study
  - Registry studies
  - Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA #                      BLA 125469  
Product Name:                TRULICITY (dulaglutide)

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PMR/PMC Description:      A medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Trulicity (dulaglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Trulicity (dulaglutide).

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	June 2015
	Study/Trial Completion:	<hr/> December 2030
	Final Report Submission:	<hr/> March 2032

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Based on nonclinical studies Glucagon-like peptide-1 (GLP-1) agonists have been associated with thyroid C-cell tumors.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the registry is to detect the majority of cases of medullary thyroid carcinoma (MTC) which occur in the United States over the 15 year period after marketing approval of dulaglutide, to evaluate all cases for risk factors for MTC and for exposure to diabetes medications, and to determine whether there is a relationship between dulaglutide exposure and risk for MTC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A case series registry that seeks to identify all possible cases of MTC that occur in North America during the fifteen year period after approval of dulaglutide. Ascertainment of cases should be as extensive as possible, including such sources as cancer registries; cancer center hospitals; medical centers with endocrinology fellowship programs; and professional organizations such as the American Thyroid Association, North American members of the International Thyroid Oncology Group, the Endocrine Society, and the American Association of Clinical Endocrinologists. All cases will be evaluated for risk factors for MTC and for exposure to dulaglutide or other diabetes medications. Analyses will be conducted to determine whether dulaglutide appears to be a risk factor for MTC. Reporting is to occur annually.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA #                    BLA 125469

Product Name:                Dulaglutide

PMR/PMC Description:      A 26-week randomized, controlled trial comparing once weekly Trulicity (dulaglutide), 0.75 mg and 1.5 mg, with insulin glargine on glycemic control in patients with type 2 diabetes mellitus and moderate or severe renal impairment, with a 26-week controlled extension.

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PMR/PMC Schedule Milestones:

Study/Trial Completion:

November 2016

Final Report Submission:

May 2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Dulaglutide was reasonably safe in patients with mild to moderate renal impairment in the phase 2 and phase 3 trials. This PMR will further evaluate safety in the subpopulation of patients with moderate or severe renal impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Though dulaglutide appears to be reasonably safe in patients with mild to moderate renal impairment, there was a suggestion of dose-dependent adverse events in this sub-population. Additionally, the size of the sub-population with renal impairment evaluated in the clinical program was small. This study is designed to explore the safety and efficacy of two doses of dulaglutide compared to an active comparator in patients with moderate or severe renal impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, controlled study in patients with type 2 diabetes mellitus and with moderate or severe renal impairment.
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA #                      BLA-125469  
Product Name:                 TRULICITY (dulaglutide)

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PMR/PMC Description:      A randomized, double-blind, placebo-controlled trial evaluating the effect of Trulicity (dulaglutide) on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) observed with dulaglutide to that observed in the placebo group is less than 1.3. The trial must also assess the following adverse events: thyroid cancer, pancreatic cancer, pancreatitis, immune-mediated reactions (including serious hypersensitivity reactions), serious hypoglycemic events, hepatic events, serious gastrointestinal events, clinically significant supraventricular arrhythmias, clinically significant conduction disorders and worsening renal function.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>June 2015</u>
	Study/Trial Completion:	<u>June 2019</u>
	Final Report Submission:	<u>March 2020</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Patients with diabetes mellitus are at increased risk of cardiovascular events and cardiovascular death. There are concerns surrounding anti-diabetics that though they improve glycemic control that they may actually increase the risk of cardiovascular events/death. As part of the development of new anti-diabetic agents, sponsors have been required to meet a prespecified cardiovascular risk margin. An estimate of cardiovascular risk derived from a meta-analysis of cardiovascular data across Phase 2 and 3 programs has provided sufficient evidence that dulaglutide does not unacceptably increase cardiovascular risk above the pre-approval risk margin specified in the FDA Guidance to Industry. The Guidance also stipulates a more stringent risk margin would need to be demonstrated post-approval. This study is intended to fulfill that requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To support approvability and continued marketing, sponsors of unapproved drugs and biologics developed for the treatment of type 2 diabetes mellitus should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk as recommended in the 2008 Guidance to Industry, “Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.” This trial is intended to demonstrate that dulaglutide therapy does not result in an unacceptable increase in risk for MACE, i.e., non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.

The applicant has already provided sufficient evidence that dulaglutide does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded an unacceptable level of cardiovascular risk. Therefore, consistent with the above guidance, the primary objective of the required postmarketing trial is to establish that the upper bound of the 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with dulaglutide to that observed with placebo is less than 1.3.

Signals for thyroid cancer, pancreatic cancer, pancreatitis, immune-mediated reactions (including serious hypersensitivity reactions), serious hypoglycemic events, hepatic events, hepatic enzyme elevations, serious gastrointestinal events, clinically significant supraventricular arrhythmias, clinically significant conduction disorders, and worsening renal function will also be further assessed in this trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

**Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

**Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

**Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, placebo-controlled clinical trial evaluating the effect of dulaglutide on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus at high risk of cardiovascular disease. The primary endpoint will be the time to first occurrence of any of the following adjudicated components of cardiovascular death, non-fatal MI, and non-fatal stroke.

The long-term effects of dulaglutide on the incidence of thyroid cancer, pancreatic cancer, pancreatitis, immune-mediated reactions (including serious hypersensitivity reactions), serious hypoglycemic events, hepatic events, serious gastrointestinal events, clinically significant supraventricular arrhythmias, clinically significant conduction disorders, and worsening renal function will also be further assessed in this trial.

Required

- Observational pharmacoepidemiologic study
  - Registry studies
  - Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
  
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

---

NDA/BLA #                      BLA 125469  
Product Name:                TRULICITY (dulaglutide)

---

PMC #1 Description:        To re-evaluate dulaglutide drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process.

---

PMC Schedule Milestones:

Final Report Submission:	<u>June 2018</u>
Other:	_____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Substance release and shelf-life specifications approved under the BLA are sufficient to ensure adequate quality and safety of dulaglutide for the initial marketed product. *Additional* manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Dulaglutide Drug Substance release and shelf-life specifications are based on clinical and manufacturing experience *provided in the BLA and assessed* during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)



3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)



3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Reevaluation of (b) (4) a product specific extractables and leachables study.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

---

NDA/BLA # BLA 125469

Product Name: TRULICITY (dulaglutide)

---

PMC #4 Description: To reassess the dulaglutide drug substance and drug product control strategy, and the reference standard qualification/requalification programs, with regards to Fc region modifications and their impact on PK, including neonatal Fc binding.

---

PMC Schedule Milestones:

Final Report Submission:

December 2016

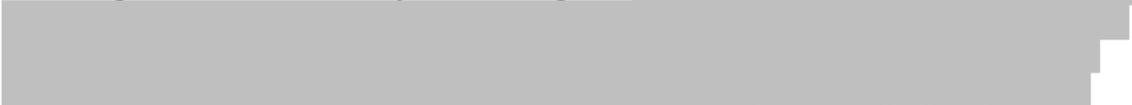
- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Discussions were held with the sponsor during the review, which led to the inclusion of additional regulatory commitments for process parameters and substantially tightened specifications due to the inadequate consideration of Fc modifications on product performance. Data was provided which demonstrate that release and stability specifications for tests which assess Fc modifications will limit Fc modifications to ranges observed during clinical development. Therefore, there is no concern with respect to product performance.

2. Describe the particular review issue and the goal of the study.

Dulaglutide is a homodimer fusion protein comprising the GLP peptide, a linker, and a modified Fc from an IgG4 monoclonal antibody. The Fc fragment (b) (4)  
  
The study will allow for reassessment of the entire control strategy for this attribute, including potentially more clinically relevant specifications.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

A reassessment of the control strategy for Fc modifications, including an assessment of their impact on neonatal Fc binding.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review microbiologist and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

---

BLA # BLA 125469  
Product Name: TRULICITY (dulaglutide)

---

PMC Description: Provide data from one additional (b) (4) batch to support the (b) (4) hour hold time limit (b) (4). Provide this data in the first annual report.

---

PMC Schedule Milestones:  
Final Report Submission: November 2015

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAR OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor has data from two batches to support the (b) (4) hour hold time (b) (4) of the drug product. Other aspects of microbial control of the drug product manufacturing process were reviewed and found adequate.

2. Describe the particular review issue and the goal of the studies.

The goal of commercial-scale hold time validation studies is to demonstrate that microbial control of the process is adequate even when (b) (4) material is held for the maximum allowable time. These studies are performed during manufacture of three different batches of product. The sponsor has data from only two batches to support the proposed maximum hold time (b) (4).

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon studies:

The sponsor will perform (b) (4) testing on (b) (4) drug product held for at least (b) (4) hours (b) (4). .
--

5. To be completed by the Product Quality Microbiology Team Leader:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)



3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon studies:

The sponsor will review temperature data and analytical testing results from commercial shipments of the semi-finished syringe and the pre-filled syringe from the (b) (4) site to the Eli Lilly site in the summer and winter.

5. To be completed by the Product Quality Microbiology Team Leader:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review microbiologist and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

---

BLA # 125469  
Product Name: Trulicity (dulaglutide)

PMC Description: Explore alternative endotoxin test methods and develop a more suitable endotoxin release test for dulaglutide drug substance and drug product.

PMC Schedule Milestones: Protocol Submission: March 2015  
Final Report Submission: December 2016

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The endotoxin release test method (b) (4)  


Additional studies should be conducted to determine the suitability of alternative endotoxin release test methods. These studies are not required pre-approval because: (1) the test method accurately measures endotoxin (b) (4) in the drug substance manufacturing process; (2) an endotoxin control strategy is in place for the drug product manufacturing process; and (3) (b) (4) appears to correspond with (b) (4)  


2. Describe the particular review issue and the goal of the studies.

The sponsor should: (1) determine whether alternative endotoxin test methods can accurately detect endotoxin in the product; and (2) modify or change the endotoxin test method if a more suitable method is identified. The PMC studies may lead to the identification or development of a more suitable endotoxin release test method for this product.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon studies:

The sponsor will submit the PMC study protocol and the PMC final study report for (b) (4) studies performed for the drug substance and drug product. The sponsor will modify or change the endotoxin release test method based on the PMC study data, if applicable.

5. To be completed by the Product Quality Microbiology Team Leader:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

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/s/  
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JENNIFER R PIPPINS  
09/18/2014

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: August 21, 2014

TO: Jean-Marc P. Guettier, M.D.  
Director,  
Division of Metabolism and Endocrinology Products  
(DMEP)  
Office of New Drugs (OND)

FROM: Xingfang Li, M.D., RAC  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
and  
William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIRs covering BLA 125469 (Dulaglutide,  
solution for injection) sponsored by Eli Lilly and  
Company, U.S.A.

At the request of the Division of Metabolism and Endocrinology Products (DMEP), Office of New Drugs (OND), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence study.

**Study Number#:** H9X-MC-GBDT

**Study Title:** "Comparative Pharmacokinetics of Dulaglutide after Administration via an Auto-injector and a Manual Syringe in Healthy Subjects"

The audits included a thorough examination of facilities and equipment, reviews of study records including correspondence, and interviews and discussions with facility management and staff.

**Clinical:**

The clinical portion of the study was audited at Covance CRU, Inc., Daytona Beach, FL by Brunilda Torres (ORA Investigator, FLA-DO) during June 2-5, 2014. Following the inspection at the clinical site, there were no objectionable findings during the inspection and Form FDA-483 was not issued.

**Bioanalytical:**

The analytical portion of the study was audited (b) (4) by (b) (4) (ORA Investigator, BLT (b) (4)) and OSI Scientist Dr. (b) (4) during (b) (4). Following the inspection at the analytical site, there were no objectionable findings during the inspection and Form FDA-483 was not issued.

**Conclusion:**

Following review of the inspectional findings, I recommend that:

- The results from the clinical and bioanalytical portions of study H9X-MC-GBDT are acceptable for further Agency review.

Xingfang Li, M.D., RAC  
Division of Bioequivalence and GLP compliance  
Office of Scientific Investigations

**Final Classifications:**

**NAI: Covance CRU, Inc., Daytona Beach, FL**  
**FEI: 3004834650**

**NAI: (b) (4)**  
**FEI: (b) (4)**

cc:

OSI/DBGLPC/Taylor/Haidar/Skelly/Choi/Li

OSI/DBGLPC/Bonapace/Dasgupta

OSI/DBGLPC/Fenty-Stewart/Nkah/Dejernett/Johnson

CDER/OND/OMDP/Guettier/Adeolu

ORA/FLA-DO/HFR-SE250/Sinninger

ORA/FLA-DO/HFR-SE250/Torres

ORA (b) (4) DO/HFR-CE840/ (b) (4)

ORA (b) (4) DO/HFR-CE250/ (b) (4)

ORA (b) (4) DO/HFR-CE2425/ (b) (4)

Draft: XFL 8/21/2014

Edit: MFS 8/22/2014; SHH 8/24/2014

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ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical  
Sites/ (b) (4)

File # BE6592

**FACTS:** 8733602

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/s/  
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XINGFANG LI  
08/28/2014

SAM H HAIDAR  
08/29/2014

WILLIAM H TAYLOR  
09/02/2014



**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research**

Division of Monoclonal Antibodies  
Office of Biotechnology Products

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## **FINAL LABEL AND LABELING REVIEW**

**Date:** August 29, 2014

**Reviewer:** Jibril Abdus-Samad, PharmD, Labeling Reviewer  
Division of Monoclonal Antibodies (DMA)

**Through:** Joel Welch, PhD, Product Quality Reviewer  
Sarah Kennett, PhD, Review Chief  
Division of Monoclonal Antibodies (DMA)

**Application:** BLA 125469

**Product:** Trulicity™ (dulaglutide)

**Applicant:** Eli Lilly and Company

**Submission Dates:** September 18, 2013; May 6, 2014; July 17, 2014; and August 27, 2014

### **Executive Summary**

The container labels and carton labeling for Trulicity™ (dulaglutide) were reviewed initially and found not to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia, [8/1/2014 – 11/30/2014]. Labeling deficiencies were identified, mitigated, and resolved. The container labels and carton labeling submitted on August 27, 2014 are acceptable. Approval is recommended.

### **Background and Summary Description**

BLA 125469 Trulicity™ (dulaglutide) was submitted on September 18, 2013. Trulicity™ is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended initial dosage is 0.75 mg subcutaneously once weekly. The dose can be increased to 1.5 mg subcutaneously once weekly

for additional glycemic control. Trulicity™ is available in the following dosage forms and strengths:

Pen

- Injection: 0.75 mg/0.5 mL solution in a single-dose Pen
- Injection: 1.5 mg/0.5 mL solution in a single-dose Pen

Prefilled Syringe

- Injection: 0.75 mg/0.5 mL solution in a single-dose prefilled syringe
- Injection: 1.5 mg/0.5 mL solution in a single-dose prefilled syringe

**Materials Reviewed:**

- Prefilled Syringe Container Labels: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL
- Pen Container Labels: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL
- Prefilled Syringe Carton: Labeling 0.75 mg/0.5 mL and 1.5 mg/0.5 mL
- Pen Carton Labeling: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL

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Start of Sponsor Material



18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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JIBRIL ABDUS-SAMAD  
08/29/2014

JOEL T WELCH  
08/29/2014

SARAH B KENNETT  
08/29/2014

# Internal Consult

\*\*\*\*Pre-decisional Agency Information\*\*\*\*

**Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.**

To: Naomi Redd, Risk Management Analyst, DRISK

From: Tara Turner, Regulatory Review Officer, OPDP

CC: Tara Turner, Regulatory Review Officer, OPDP  
Adora Ndu, Team Leader, OPDP  
Lyle Canida, SRPM, OSE  
Doris Auth, Acting Team Leader, DRISK  
Naomi Redd, Risk Management Analyst, DRISK  
Kate Heinrich Oswell, Health Communications Analyst, DRISK  
Carole Broadnax  
CDER-OPDP-RPM  
Michael Wade, RPM, OPDP

Date: August 25, 2014

Re: BLA # 125469  
TRULICITY (dulaglutide) injection, for subcutaneous use  
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)  
Materials (Submission date: June 30, 2014)

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## **Materials Reviewed**

OPDP has reviewed the following proposed REMS materials for TRULICITY:

- Healthcare Provider (HCP) REMS Materials:
  - REMS letter for Healthcare Professional (print version)

- REMS letter for Healthcare Professional (email version)
- REMS letter for Professional Societies (print version)
- REMS letter for Professional Societies (email version)
- REMS Fact Sheet
- REMS Website Landing Page

The version of the draft REMS materials used in this review were emailed by Naomi Redd on August 14, 2014, and is attached to the end of this review.

The version of the proposed draft PI that was used for this review was obtained from the DMEP SharePoint site on August 13, 2014, entitled “Dulaglutide BLA125469 USPI response 1 to FDA Aug 1 2014.docx”.

OPDP offers the following comments on these draft REMS materials for TRULICITY.

### **General Comments**

Please remind Eli Lilly and Company (Lilly) that REMS materials are not appropriate for use in a promotional manner.

OPDP notes that the Trulicity PI is still being reviewed and modified. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved PI.

OPDP cannot comment on place holders such as “[www.TRULICITYREMS.com](http://www.TRULICITYREMS.com)”. However, we recommend that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Lilly that the REMS specific website should not be the sole source of approved REMS materials.

### **REMS Materials**

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Healthcare Provider (HCP) REMS Materials:
  - REMS letter for Healthcare Professional (print version)
  - REMS letter for Healthcare Professional (email version)
  - REMS letter for Professional Societies (print version)
  - REMS letter for Professional Societies (email version)
  - REMS Fact Sheet
  - REMS Website Landing Page

### **Specific Comments**

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS pieces:

- **REMS letter for Healthcare Professional (print version), REMS letter for Healthcare Professional (email version), REMS letter for Professional Societies (print version), REMS letter for Professional Societies (email version), and REMS Fact Sheet**
  - OPDP is concerned that the section of these REMS materials entitled “Indication” implies that this is the full indication for Trulicity; however, it omits material information from the full indication, which includes the limitations of use for Trulicity. We acknowledge that one limitation of use for Trulicity is presented (“Trulicity is not recommended as first-line therapy for patients with type 2 diabetes mellitus inadequately controlled on diet and exercise”). However, this is not sufficient to correct the misleading impression. OPDP recommends revising the “Indication” section of these REMS materials to communicate the **full** indication, which includes **all** of the limitations of use for Trulicity.
  
- **REMS letter for Healthcare Professional (print version), REMS letter for Healthcare Professional (email version), REMS letter for Professional Societies (print version), and REMS letter for Professional Societies (email version)**
  - OPDP is concerned that the risk presentation included in the section titled “Risk of (b) (4) Pancreatitis” uses language that is not consistent with the draft prescribing information (PI) for Trulicity. Specifically, these REMS materials state (b) (4). However, Section 1.1 (Limitations of Use) and Section 5.2 (Warnings and Precautions) of the draft PI states “Consider other antidiabetic therapies for patients with a history of pancreatitis”. OPDP recommends revising this risk presentation for consistency with the draft PI.
  
- **REMS letter for Healthcare Professional (print version), REMS letter for Healthcare Professional (email version), REMS letter for Professional Societies (print version), REMS letter for Professional Societies (email version), and Website Landing Page**
  - **“Potential Risk of Medullary Thyroid Carcinoma (MTC).** Thyroid C-cell tumors have been observed in rodent studies with other glucagon-like peptide (GLP-1) receptor agonists. It is unknown whether TRULICITY causes thyroid C-cell tumors, including MTC in humans.” (bolded emphasis original)
    - OPDP is concerned that this presentation minimizes the risks associated with Trulicity by omitting important material information regarding thyroid C-cell tumors. Specifically, Section 17.1 (Patient Counseling Information) of the draft PI states, (b) (4)

(b) (4)  
OPDP recommends revising this presentation to include this important material information in a manner consistent with the draft PI.

- **“Risk of (b) (4) Pancreatitis.”** (b) (4) pancreatitis has been reported with the use of GLP-1 receptor agonists. Cases of (b) (4) pancreatitis have been described in association with TRULICITY during clinical trials.

(b) (4)  
” (bolded emphasis original)

- OPDP is concerned that this presentation minimizes the risks associated with Trulicity by omitting important material information regarding (b) (4) pancreatitis.

(b) (4)  
OPDP recommends revising this presentation to include this important material information in a manner consistent with the draft PI.

- OPDP is concerned that the statement (b) (4) minimizes the risk of pancreatitis associated with Trulicity by dissociating this risk from the drug. OPDP recommends deleting this statement.

- OPDP is concerned that the Website Landing Page omits material information about the risk of (b) (4) pancreatitis. Specifically, Section 5.2 (Warnings and Precautions) of the draft PI states, “If pancreatitis is suspected, promptly discontinue TRULICITY. If pancreatitis is confirmed, TRULICITY should not be restarted. TRULICITY has not been evaluated in patients with a prior history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.” OPDP recommends revising this presentation to include this important material information in a manner consistent with the draft PI.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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TARA P TURNER  
08/25/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: August 22, 2014

To: Jean-Marc Guettier, MD  
Director  
**Division of Metabolism and Endocrinology Products  
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, MSN, FNP-BC, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Tara Turner, Pharm.D., MPH  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFUs)

Drug Name (established name): TRULICITY (dulaglutide)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: BLA 125469

Applicant: Eli Lilly and Company

## 1 INTRODUCTION

On September 17, 2013, Eli Lilly and Company submitted for the Agency's review a Biologics Licensing Application (BLA 125469) for TRULICITY (dulaglutide) injection, for subcutaneous use, a glucagon-like peptide (GLP-1) agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on September 23, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for TRULICITY (dulaglutide) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs was completed on March 19, 2014.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DMEP under separate cover.

## 2 MATERIAL REVIEWED

- Draft TRULICITY (dulaglutide) MG and IFUs received on May 06, 2014, and received by DMPP on August 14, 2014.
- Draft TRULICITY (dulaglutide) MG and IFUs received on May 06, 2014, and received by OPDP on August 13, 2014.
- Draft TRULICITY (dulaglutide) Prescribing Information (PI) received on September 18, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on August 14, 2014.
- Draft TRULICITY (dulaglutide) Prescribing Information (PI) received on September 18, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on August 13, 2014.
- Approved TANZEUM (albiglutide) comparator labeling dated April 15, 2014.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG and IFUs the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10 and the IFU documents using the Verdana font, size 11.

In our collaborative review of the MG and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

#### **4 CONCLUSIONS**

The MG and IFUs are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
08/22/2014

TARA P TURNER  
08/22/2014

MELISSA I HULETT  
08/22/2014

LASHAWN M GRIFFITHS  
08/22/2014

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

## **Memorandum**

**Date:** August 20, 2014

**To:** Abolade (Bola) Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Tara Turner, Pharm.D., MPH  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Through:** Melinda McLawhorn, PharmD, BCPS  
Regulatory Review Officer, OPDP

**CC:** Adora Ndu, Pharm.D., Team Leader, OPDP

**Subject:** **BLA 125469**  
**TRULICITY (dulaglutide) injection, for subcutaneous use**

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On September 23, 2013, DMEP consulted OPDP to review the draft Package Insert labeling (PI), carton and container labeling, Medication Guide (MG), and Instructions for Use (IFU) for TRULICITY (dulaglutide) injection, for subcutaneous use (Trulicity) for the original BLA submission.

OPDP reviewed the proposed substantially complete version of the PI provided by DMEP via their SharePoint site on August 13, 2014, and the MG and IFU submitted to the electronic document room on May 6, 2014. OPDP also reviewed the proposed carton and container labeling provided via e-mail from DMEP on August 15, 2014. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the MG and IFU for Trulicity under separate cover. OPDP's comments on the PI and carton and container labeling are provided below.

Thank you for your consult. If you have any questions about OPDP's comments, please contact Tara Turner at 6-2166 or at [Tara.Turner@fda.hhs.gov](mailto:Tara.Turner@fda.hhs.gov).

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/s/  
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TARA P TURNER  
08/20/2014



Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**CDRH Human Factors Consult Review**

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

DATE: June 19, 2014

FROM: QuynhNhu Nguyen, Human Factors Specialist, CDRH/ODE/DAGRID  
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID  
TO: Suchitra Balakrishnan, Clinical Analyst, CDER/OND/ODEII/DMEP  
Abolade Adeolu, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **BLA 125469**  
Applicant: Eli Lilly and Company  
Drug Constituent: Dulaglutide  
Device Constituent: Single-Use Pen and Prefilled Syringe  
Intended Use: improve glycemic control in type 2 diabetes mellitus  
CDRH CTS Tracking No.: 1300528

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QuynhNhu Nguyen, Combination Products Human Factors Specialist

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Ron Kaye, Human Factors and Device Use-Safety Team Leader

## **CDRH Human Factors Review**

### ***Combination Product Device Information***

Submission No: BLA 125499

Applicant: Eli Lilly and Company

Drug Constituent: Dulaglutide

Device Constituent: Single-Use Pen and Prefilled Syringe

Intended Use: improve glycemic control in type 2 diabetes mellitus

### ***CDRH Human Factors Involvement History***

- 9/23/2014: CDRH HFPMET was requested to review the human factors study reports for the single use pen and prefilled syringe
- 3/3/2014: CDRH HFPMET provided two deficiencies identified from the review of the study reports regarding the lack of differentiation study and study results. These deficiencies were included in the Mid-Cycle communication letter to Eli Lilly.
- 4/21/2014: CDRH HFPMET received the Sponsor's response to the deficiencies identified in the Mid-Cycle communication regarding the study results (SN0018).
- 5/27/2014: CDRH HFPMET received the Sponsor's response to the deficiencies identified in the Mid-Cycle communication regarding the differentiation study (SN0024).
- 6/20/2014: CDRH HFPMET provided final review recommendation to CDER project manager.

### ***Overview and Recommendations***

The Division of Metabolism and Endocrinology Products, Office of New Drugs, Center for Drugs Research and Evaluation requested a consultative review on the human factors validation study reports contained in the BLA submitted by Eli Lilly. The device constituents are prefilled syringe and peninjector for delivery of dulaglutide for improve glycemic control in type 2 diabetes mellitus.

Results of the single use pen (SUP) and prefilled syringe (PFS) human factors validation study showed multiple failures on critical tasks across different user groups and these failures could result in patient harm (needle stick injuries, injection into the intramuscular space, reduced drug efficacy, etc.) In SN0018, Eli Lilly provided the description and root cause analysis for each use error observed, the clinical relevance if the use error were to occur, and the mitigations. Lilly noted that the study demonstrated a high rate of success for participants who received training. Lilly proposes that labeling in the US Package Insert instruct HCPs to train patients on the correct use of the devices. Lilly does not see a need for an additional 15-person validation study. This consultant request the medical officers on the team to review this response, specifically, the clinical significance discussion for each use error to determine if that is acceptable. This consultant received email responses indicating that they found the response acceptable, and did not have any comments. In addition, this consultant also requested a consult from a CDRH medical officer regarding this response. This medical officer noted that review of the Sponsor's responses show that the majority of use errors were a result of inadequate training in subjects who were untrained to pen use or confusion in subjects who had previous experience with pen use for insulin injection. Those subjects who had been trained had a high rate of success.

Therefore, the Sponsor should be encouraged to ensure that the labeling include appropriate instructions for use for the patient, and notation in the HCP labeling regarding the requirement for training by the HCP prior to use of the device. GLP-1 agonists influence glycemic control by affecting the rate of gastric emptying. While incorrect dosing, error in injection resulting in over-dosing or under-dosing, may result in some loss of glycemic control it is unlikely that serious or severe hypoglycemia or hyperglycemia would result.

There was no differentiation study for the two strengths available with other competitor's products for both the pen and prefilled syringe configuration. In SN0024, Eli Lilly reported that a differentiation study (Study H8L-MC-IQCP) was conducted to demonstrate that the intended users of the dulaglutide SUP and PFS can effectively differentiate the 1.5 mg and 0.75 mg dose strengths in the intended use environment. The study results were found to be acceptable.

**Recommendation:** Based on the input received from the medical officers, this consultant found the results of the human factors validation studies and the Sponsor's response to the IR acceptable. This consultant accepts Lilly's proposal to ensure that labeling in the US Package Insert instruct HCPs to train patients on the correct use of the devices, and specify training as requirement in the labeling. The additional differentiation study report was also found acceptable.

## Appendix 1: Evaluation of Review Correspondences (Information Requests)

### *Evaluation of First Correspondence (IR sent on 3/26/2014, response received SN0018)*

1. There was no differentiation study for the two strengths available with other competitor's products for both the pen and prefilled syringe configuration. Please provide us results of a study focusing on evaluating the differentiating aspects for both the pen and prefilled syringe configuration, and demonstrating that representative users can identify and select the correct product.

**Summary and Evaluation of Eli Lilly's Response:** A differentiation study will be conducted and the study report will be submitted for review.

2. Results of the pen and prefilled syringe human factors validation study showed multiple failures on critical tasks across different user groups and these failures could result in patient harm (needle stick injuries, injection into the intramuscular space, reduced drug efficacy, etc.) We believe that additional mitigations are necessary, and we need to review results demonstrating that the mitigations improve user's ability to use the device safely and effectively.
  - a. For the prefilled syringe configuration, we are most concerned with failures to inspect the device and check expiration date, selecting improper injection site, failures to insert the needle at <sup>(b) (4)</sup> degrees, and disposing the product improperly.
  - b. For the pen configuration, we are most concerned with failures to check expiration date and ensure that the drug product is clear (not cloudy), reattaching the base cap, selecting improper injection site, and failures to press the button down to ensure full dose delivery.

**Summary and Evaluation of Eli Lilly's Response:** Eli Lilly provided detailed response to clarify why they do not believe the use errors seen in the HF studies represent patient harm.

#### Prefilled Syringe Issues:

- Use Error – Failure to Check Expiration Date: Eli Lilly clarified that the clinical consequences of a patient not checking the expiration date were evaluated. In the worst-case scenario, the patient would inject expired drug product. Injecting an expired drug has the theoretical consequence of injecting a drug that has lost partial potency (which could result in mild, symptomatic or asymptomatic hyperglycemia) or a drug that has degraded and developed residual components. Lilly asserts that the training, which showed a substantial decrease in these use errors, along with the IFU directing the user to check the expiration date, provides adequate assurance that patients have the correct medicine and that it has not expired. Lilly does not believe that additional changes in the device user interface would further reduce or eliminate the likelihood of this use error.
- Use Error – Selects Improper Injection Site: Eli Lilly reported that the clinical consequences of selecting the improper injection site were evaluated. Injecting in a site other than the sites recommended in the IFU could lead to an intramuscular (IM) injection. Study H9X-MC-GBDR (GBDR) demonstrated that systemic exposure to dulaglutide was similar via SC and IM dose administration routes. Lilly asserts that this is a use error common to all injection delivery devices and

the mitigations implemented to reduce its occurrence are appropriate and adequate.

- Use Error – Failure to insert the Needle at 45 Degrees: Eli Lilly indicated that the clinical consequences of failing to insert the needle at a 45-degree angle were evaluated. Inserting the needle at a 45-degree angle is recommended as inserting the needle at an angle greater than 45 degrees could result in an IM injection. (b) (4)  
[REDACTED] (b) (4)  
Study GBDR demonstrated that systemic exposure to dulaglutide was similar via SC and IM dose administration routes. Dulaglutide was well tolerated when administered via SC and IM injection routes.
- Use Error – Improper Disposal: Eli Lilly reported that the clinical consequences of improper disposal related to needle stick injuries were evaluated. If the needle stick occurs in someone other than the patient and the needle is contaminated with a blood-borne pathogen, it is possible that the blood-borne pathogen could be transferred. The potential harm is serious, but the probability of this harm occurring is very low.

Single Use Peninjector Issues:

- Use Error – Failure to Check Expiration Date: Eli Lilly clarified the clinical consequences of failure to check for expiration date were evaluated. In the worst-case scenario, the patient would inject expired drug product. Injecting an expired drug that has lost partial potency is not likely to be noted by most users and may result in mild, symptomatic or asymptomatic hyperglycemia. If the expired medication has degraded and developed residual components, injecting the expired medication could lead to the injection of drug degradation products.
- Use Error – Failure to Check that Medication is Clear, not Cloudy: Eli Lilly reported that the clinical consequences of failure to check the medication were evaluated. If the user does not inspect the medicine in the SUP, it is possible not to notice that the medicine is cloudy, discolored, or has particles in it. Lilly has not observed degradation that has led to visibly cloudy, discolored or particulates in the solution for Trulicity under normal storage conditions, accelerated temperature storage studies, or in-use period stability testing (CTD Module 3.2.P.8.3.1, Primary Stability Data). After analyzing the probability of occurrence, controls (taking into account the IFU instruction to inspect the medication), and severity of harm for this use error, Lilly determined the risk level to be acceptable.
- Lilly believes that failing to check the condition of a solution medication is a use error that is common to all drug delivery devices and that the mitigations implemented to reduce its occurrence are appropriate and adequate. Lilly asserts that the training along with the IFU, which showed a substantial decrease in these use errors.
- Use Error – User Replaces Base Cap: Eli Lilly indicated that the clinical consequences of replacement of the Base Cap were evaluated. If the Base Cap is incorrectly replaced prior to the injection, it can cause the needle to bend; there is also a possibility of a needle stick injury. A bent needle has the potential of causing a painful injection and minor injection-site trauma. (b) (4)

[REDACTED] if the needle is

sufficiently bent, it may not even penetrate the skin. The needle can also be bent to the point where it is crimped and the medication will not be delivered. If the Base Cap is incorrectly replaced after the injection, the risk is the possibility of a needle-stick injury. Lilly asserts that the training along with the IFU, which showed a substantial decrease in these use errors.

- Use Error – Selects Improper Injection Site: Eli Lilly reported that the clinical consequences of selecting an improper injection site were evaluated in Study GBDR. Injecting in a site other than the sites recommended in the IFU could lead to an IM injection. Study GBDR demonstrated that systemic exposure to dulaglutide was similar via SC and IM dose administration routes.
- Use Error – Incomplete Button Press: Eli Lilly stated that the device is designed to provide audible and tactile feedback when the Injection Button is fully depressed. Lilly asserts that the mitigations implemented to reduce the occurrence of incomplete button press are appropriate. Lilly does not believe that additional changes in the device user interface are necessary to further reduce or eliminate the likelihood of this use error.

### ***Evaluation of Second Correspondence (Response received SN0024)***

In SN0024, Eli Lilly reported that a differentiation study (Study H8L-MC-IQCP) was conducted to demonstrate that the intended users of the dulaglutide SUP and PFS can effectively differentiate the 1.5 mg and 0.75 mg dose strengths in the intended use environment.

### **Summary and Evaluation of Eli Lilly's Response:**

Device differentiation testing involved two (2) randomly ordered scenarios, including strength differentiation (that is, selecting a dulaglutide device of the prescribed strength when presented with a choice of both the 1.5 mg and 0.75 mg dose strengths) and competitor differentiation (that is, selecting a dulaglutide device of the prescribed strength when presented with a group of other devices used for the treatment of diabetes).

There was one use error observed during the PFS device differentiation tasks. This use error involved a Subject selecting an insulin pen (KwikPen) instead of the PFS. This one observed device differentiation error was caused by a mental model mismatch between the task and the Subject's own experience. This Subject had never used a syringe of any kind, and thus disregarded the PFS altogether and selected the only other pen device that was not his own device. In both instances of carton differentiation use error, Subjects selected the correct dose strength, but incorrect device type. Both Subjects selected the correct device type in 1 of the 2 tasks, but selected the incorrect device type in the other task. The Subjects focused primarily on dose strength and did not realize that there was more than 1 device type.

## Appendix 2: Summary of Human Factors Validation (Summative) Study Reports

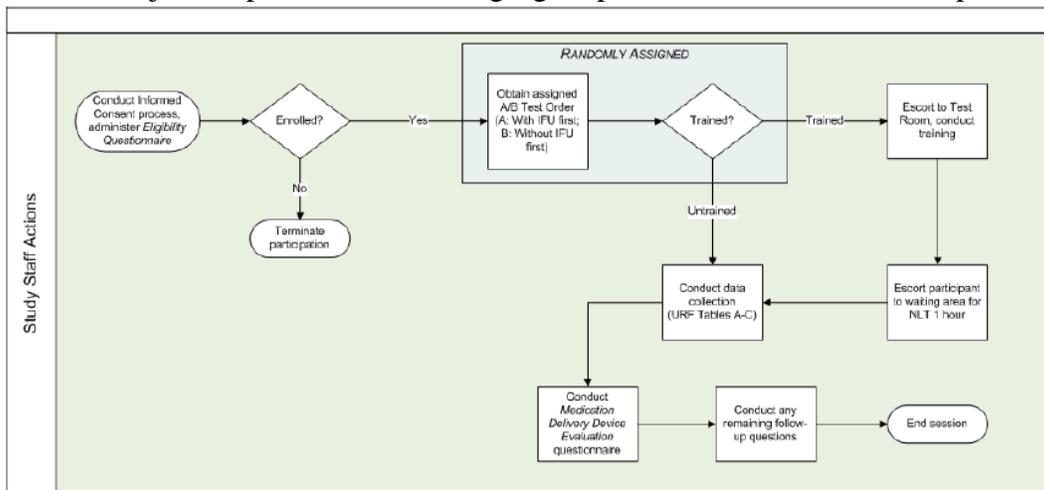
### *Prefilled Syringe Study*

Eli Lilly stated that due to the extensive experience base relating to usability of manual syringes, formal formative human factors studies were not conducted during the course of developing the dulaglutide PFS due to the following factors:

- The design is an instance of a commercially available (b) (4) platform.
- The PFS has been used in multiple clinical trials with dulaglutide self-administration. There is a known potential use error in which the user bent the needle by recapping before use. The user recognized that the needle was bent and did not attempt to inject. The commercial instructions for use clearly inform the user not to recap the syringe.
- The preliminary hazard analysis and AFMEA did not indicate any significant usability issues that needed to be better understood through formative testing.

A summative human factors study was performed as validation testing for the dulaglutide prefilled syringe. The participants were asked to perform an injection of placebo into an injection pad. The protocol for the summative PFS Human Factors study was submitted to FDA for review, and the FDA feedback was incorporated prior to starting the study. Refer to FDA Meeting Request Written Response; Author: Abolade Adeolu; ref ID: 3187487.

While HCPs are intended users of the PFS, they were not included in the summative study as it is expected that HCP's use prefilled syringes to administer injections on a regular basis [Source: FDA Meeting Request Written Response; Author: Abolade Adeolu; Date: 11-Sep-2012, ref ID:3187487]. A total of 93 patient participants were included in the study. These participants were considered to be representative of the intended users of the syringe. Half of the participants received representative training, which consisted of a step-by-step demonstration of the entire injection process while pointing to each step in the IFU. The participant practiced the entire process one time, using the IFU, with the moderator assisting as necessary to ensure a successful injection into an injection pad.. The following figure provides the data collection process:



The following table provides a summary of the study results:

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
1	Remove the PFS and the IFU from the package		186 (100.0%)	Fails to/Unable to open package	0	0	0
				Fails to/Unable to remove device from package	0	0	0
				Exposes device to shock or vibration (drops, rough handling)	0	0	0
				Remove from Package - Other	0	0	0
2	Inspect the PFS to be sure it is not damaged or expired	√	104 (55.9%)	Fails to check expiration date	6	70	76
				Fails to inspect syringe for damage	6	39	45
				Inspect - Other	0	0	0
3	Wash your hands (can be simulated in this study)		99 (53.2%)	Does not wash hands	25	62	87
4	Select the injection site (injection pad will be used in this study)		177 (95.2%)	Selects improper site	2	7	9
5	Pull off and discard the needle cover		154 (82.8%)	Fails to/Unable to remove needle cover	0	0	0
				Holds syringe by plunger rod	1	0	1
				Pulls or pushes on plunger rod	1	2	3
				Fails to discard needle cover	1	29	30
				Touches needle	0	0	0
				Remove Needle Cover - Other	0	0	0
6	Gently grasp a fold of skin at the injection site (injection pad will be used in this study)		160 (86.0%)	Fails to pinch injection site	5	19	24
				Pinches inadequate amount	0	2	2

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
7	Insert the needle into the skin at about a 45 degree angle (injection pad will be used in this study)		146 (78.5%)	Needle inserted at any angle other than ~45 degrees	3	37	40
				Does not insert needle	0	0	0
				Exposes device to shock or vibration (drops, rough handling)	0	0	0
				Touches needle	0	0	0
8	Slowly push the Plunger all the way in until all the placebo is injected (injection pad will be used in this study)	√	169 (90.9%)	Starts injection before inserting needle	1	12	13
				Fails to / Unable to push the plunger	0	0	0
				Partially pushes the plunger	1	2	3
				Moves angle of syringe while pushing the plunger	1	0	1
				Give Injection – Other	0	0	0
9	Remove the needle from the skin (injection pad will be used in this study)		186 (100.0%)	Removes syringe while injecting	0	0	0
				Removes needle at different angle than inserted	0	0	0
10	Gently let go of the fold of skin (injection pad will be used in this study)		182 (97.8%)	Releases pinch before injection is complete	0	4	4
11	Dispose of the PFS in a puncture-resistant sharps container		138 (74.2%)	Improper disposal	0	31	31
				Attempts to reattach needle cover	3	35	38
				Dispose- Other	0	0	0
				Exposes device to shock or vibration (drops, rough handling)	0	0	0

## ***Peninjector Study***

During the clinical development program for dulaglutide, Eli Lilly interviewed patients and health care providers to obtain input in the context of a patient-centered design approach. Market research and market research based usability studies were conducted from 2003 to 2010 to inform the development of an autoinjector platform. The results of market research usability testing as well as a Preliminary Hazard Analysis, Intended Use Worksheet and the dulaglutide SUP AFMEA were utilized in the development of a formal human factors program in accordance with the June 2011 FDA Draft Guidance.

Prior to conducting the final human factors validation study, a formative human factors study was conducted as a simulated injection study. This study did not identify any new use errors that had not been previously evaluated in the dulaglutide use FMEA. No unique use errors were observed as a result of any tested use scenarios.

The protocol for the Human Factors validation study was submitted to FDA for review, and the FDA feedback was incorporated prior to starting the study. Refer to FDA Meeting Request Written Response; Author: Abolade Adeolu; ref ID: 3187487.

The following tables show the breakdown of the participants included in the study, and the breakdown of the trained and untrained participants:

<b>Experience Group</b>	<b>Injection Naïve Patients</b>	<b>Injection Experienced Patients</b>	<b>Caregivers</b>	<b>HCP</b>	<b>Subtotals</b>
No Impairment	17	22	29	30	98
Vision Impairments	6	5	1	--	12
Hand Impairments	5	8	--	--	13
Hand and Vision Impairments	2	3	--	--	5
Subtotals	30	38	30	30	
Total	128				

<b>Experience Group</b>	<b>Injection Naïve Patients</b>	<b>Injection Experienced Patients</b>	<b>Caregivers</b>	<b>HCP</b>	<b>Subtotals</b>
Trained	15	19	15	15	64
Untrained	15	19	15	15	64
Subtotals	30	38	30	30	
Total	128				

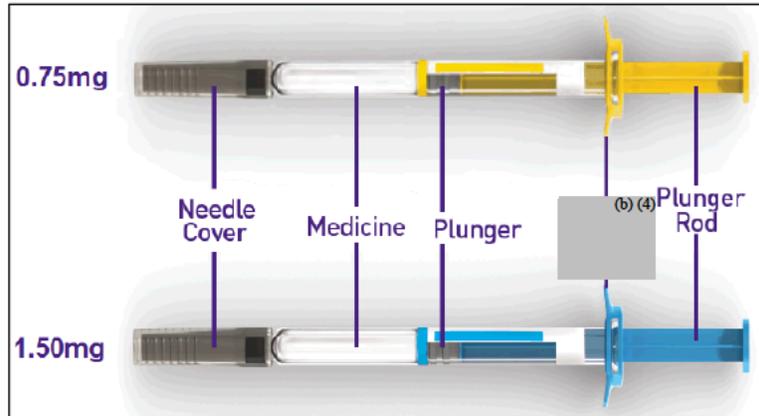
The following table shows a summary of the study results:

Step	Use Step	Critical/ Priority Task	Total Completion Rate	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
1	Remove the SUP and the IFU from the package		128/128 (100.0%)	Fails to /Unable to open package	0	0	0
				Fails to / Unable to remove device from package	0	0	0
				Exposes device to shock or vibration (drops, rough handling)	0	0	0
				Remove from package - Other	0	0	0
2	Inspect the SUP to be sure it is not damaged or expired	Priority	74/128 (57.8%)	Fails to check expiration date	3	43	46
				Fails to inspect pen for damage	1	30	31
				Fails to check drug (clear, not cloudy)	5	28	33
3	Pull off and discard the gray base cap	Critical	109/128 (85.2%)	Fails to / Unable to remove base cap	1	1	2
				Twists base cap without pulling	0	0	0
				Twists or pulls body or button & damages device or injures self	0	0	0
				Fails to discard base cap	0	17	17
				Unlocks SUP and presses button before removing base cap	1	1	2
4	Place the clear base of the SUP flat and firmly against the skin at the injection site	Priority	117/128 (91.4%)	Doesn't use bare skin	0	0	0
				Selects improper site	1	6	7
				Exposes device to shock or vibration (drops, rough handling)	0	0	0
				Unlocks and presses button before placing on skin	0	1	1
				Touches needle	0	0	0
				Places SUP upside down/inverts	0	3	3
5	Unlock by turning the lock ring		123/123 (100.0%)	Fails to unlock	0	0	0
				Exposes device to shock or vibration (drops, rough handling)	0	0	0

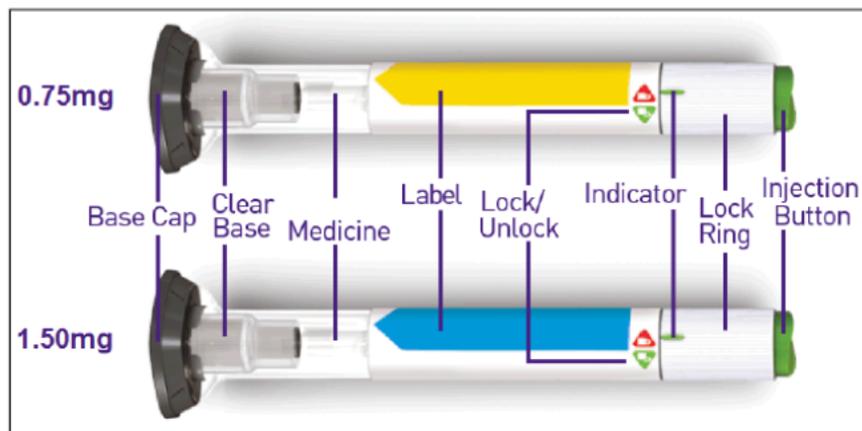
Step	Use Step	Critical/ Priority Task	Total Completion Rate	Potential Use Errors	Use Error Count		
6	Press and hold the green injection button	Priority	107/124 (86.3%)	Pinches up skin	6	10	16
				Fails to/Unable to press button	0	0	0
				Incomplete button press (does not start injection or does not stay down)	0	2	2
7	Hold the clear base of the SUP firmly against the skin until a second click is heard (this occurs within 5-10 seconds)		113/121 (93.4%)	Removes SUP before device retracts	2	6	8
				Moves or rotates SUP while injecting	0	0	0
				Injects at angle	0	0	0
8	Remove the SUP from skin after injection	Priority	121/121 (100.0%)	Moves SUP laterally before device retracts	0	0	0
				Exposes device to shock or vibration (drops, rough handling)	0	0	0
9	Dispose of SUP in a puncture-resistant sharps container	Priority	85/123 (69.1%)	Improper Disposal	1	27	28
				Attempts to re-lock device	1	4	5
				Replaces base cap	0	21	21
				Exposes device to shock or vibration (drops, rough handling)	0	0	0
				Touches needle	0	0	0

### Appendix 3: Device Description

The dulaglutide injection prefilled syringe (PFS), shown in Figure 1 below, includes the dulaglutide injection semi-finished syringe (refer to Section 3.2.P.2, Pharmaceutical Development, and Section 3.2.P.7, Container Closure System), a plunger rod, (b) (4), and label. The prefilled syringe was developed to enable patients, caregivers, or Health Care Professionals (HCPs) to manually administer a single dose, subcutaneous injection of dulaglutide.



The single-use pen, shown in figure below, includes the dulaglutide semi-finished syringe (refer to Section 3.2.P.2, Pharmaceutical Development, and Section 3.2.P.7, Container Closure System). The single-use pen was developed to enable patients, caregivers or Health Care Professionals (HCP) to administer a single dose, subcutaneous injection of dulaglutide. Safety, ease of use, convenience and reliability were the primary principles for the design of the single use pen. The single-use pen Label provides information for drug product and dosage form as well as covering the mechanical apparatus within the single-use pen. The activation end incorporates a lock feature to prevent unintentional activation and an Injection Button to start the injection sequence. The injection end of the single-use pen incorporates a Base Cap for needle shield removal and Clear Base for stable positioning at injection site with 360 degree viewing of drug product.



## Appendix 4: Clinical Input from Medical Officers

APPEARS THIS WAY ON ORIGINAL

## Nguyen, Quynh Nhu

---

**From:** Chong, William (FDA)  
**Sent:** Monday, May 19, 2014 3:44 PM  
**To:** Balakrishnan, Suchitra; Nguyen, Quynh Nhu  
**Cc:** Adeolu, Abolade  
**Subject:** RE: Dulaglutide

I don't have any additional comments.

Bill

---

**From:** Balakrishnan, Suchitra  
**Sent:** Monday, May 19, 2014 12:14 PM  
**To:** Nguyen, Quynh Nhu; Chong, William (FDA)  
**Cc:** Adeolu, Abolade  
**Subject:** RE: Dulaglutide

I'm fine with the sponsor's responses regarding the clinical consequences highlighted if okay with Bill  
<< Message: RE: Dulaglutide >>  
Bill- the email contains the document with highlighted sections

Thanks!  
Suchitra

---

**From:** Nguyen, Quynh Nhu  
**Sent:** Monday, May 19, 2014 10:53 AM  
**To:** Balakrishnan, Suchitra; Chong, William (FDA)  
**Cc:** Adeolu, Abolade  
**Subject:** RE: Dulaglutide  
**Importance:** High

Hi all,

I am trying to complete my review and following up to see if you had a chance to review and provide clinical feedback on the yellow highlighted sections that were attached in my last email?

Thank you.

Q-

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**From:** Nguyen, Quynh Nhu  
**Sent:** Thursday, May 08, 2014 3:16 PM  
**To:** Balakrishnan, Suchitra; Chong, William (FDA)  
**Subject:** RE: Dulaglutide

Hi Suchitra,

That is correct. We would like your input regarding the Sponsor's assessment for the use errors that we are concerned about based on their human factors study reports for the PFS and peninjector.

I have highlighted in yellow the sections of the Sponsor's response in the attachment.

Also, to clarify your earlier email, the Sponsor will perform the HF differentiation study, and that is acceptable to us. We expect that they will submit the results for review.

Let me know if you have any questions.

<< File: BLA 125469 HF response.pdf >>

Q-

**QuynhNhu Nguyen, MS**  
**Lieutenant Commander, U.S. Public Health Service**

Combination Products Human Factors Specialist  
Office of Device Evaluation  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
WO66, Room 2531  
Silver Spring, MD 20993  
[quynhT.nguyen@fda.hhs.gov](mailto:quynhT.nguyen@fda.hhs.gov)  
301-796-6273

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**From:** Balakrishnan, Suchitra  
**Sent:** Thursday, May 08, 2014 2:52 PM  
**To:** Nguyen, Quynh Nhu; Chong, William (FDA)  
**Subject:** FW: Dulaglutide

Quynh

My understanding is that you want us to review section 5.2, specifically regarding the sponsor's justification about clinical consequences of the errors listed for the PFS and SUP- please confirm

<< File: response.pdf >>

Suchitra

---

**From:** Balakrishnan, Suchitra  
**Sent:** Thursday, May 08, 2014 1:52 PM  
**To:** Chong, William (FDA); Nguyen, Quynh Nhu  
**Cc:** Adeolu, Abolade  
**Subject:** Dulaglutide

Hi Bill

Quynh from CDRH had some questions regarding the sponsor's response to the human factors comments about errors related to the SUP and PFS sent post Mid-cycle (SDN 18)

[\\cdsesub1\bla\eCTD\\_Submissions\STN125469](#)

The sponsor does not want to do a HF differentiation study. CDRH is fine with the sponsor's response (Quynh- please correct if otherwise) if acceptable with clinical. I did a quick preliminary review and the responses seem acceptable to me but please take a look

Thanks!  
Suchitra

## Clinical Consult

**Date:** May 26, 2014

**From:** Patricia Beaston, M.D., Ph.D., Medical Officer

**To:** Quynh Nguyen, Human Factors Reviewer

**Device:** single use pen and prefilled syringe

**Drug:** LY2189265, Dulaglutide (BLA 125469)

**Sponsor:** Eli Lilly and Company

### **Materials reviewed:** Human Factors Study

The Sponsor is developing dulaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, for the treatment of patients with type 2 diabetes. Dulaglutide (b) (4) will be given as once weekly subcutaneous injections of 1.5 mg. The Sponsor has submitted a response to issues that were raised during a Human Factors evaluation examining the use of the single use pen and prefilled syringe. This consult is focused on the Sponsor's interpretation of the clinical risks associated with these issues. Concurrence from the Primary Medical Officer for dulaglutide is recommended.

### **Types of Errors Discussed**

- Prefilled syringe
  - Failure to check expiration date
  - Selects improper injection site
  - Failure to insert the needle at 45 degrees
  - Improper disposal
- Single use pen
  - Failure to check expiration date
  - Failure to check that the medication is clear, not cloudy
  - User replaces base cap
  - Selects improper injection site
  - Incomplete button press

Review of the Sponsor's responses show that the majority of use errors were a result of inadequate training in subjects who were untrained to pen use or confusion in subjects who had previous experience with pen use for insulin injection. Those subjects who had been trained had a high rate of success. Therefore, the Sponsor should be encouraged to ensure that the labeling include appropriate instructions for use for the patient, and notation in the HCP labeling regarding the requirement for training by the HCP prior to use of the device.

GLP-1 agonists influence glycemic control by affecting the rate of gastric emptying. While incorrect dosing, error in injection resulting in over-dosing or under-dosing, may result in some loss of glycemic control it is unlikely that serious or severe hypoglycemia or hyperglycemia would result. As dulaglutide is currently under study the rates of hypoglycemia and hyperglycemia associated with its use are not known. It is recommended that the Medical Officer performing the primary review comment on the risks of over-dose or under-dose.

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/s/  
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ABOLADE ADEOLU

06/23/2014

Administratively checked into DARRTS by Project Manager on behalf of the reviewer

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance  
Division of Premarket and Labeling Compliance

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**DATE:** May 8, 2014

**TO:** Suchitra Balakrishnan, CDER, OMPT, OND, DMED  
Suchitra.Balakrishnan@fda.hhs.gov

William Chong, CDER, OMPT, OND, DMED  
[William.Chong@fda.hhs.gov](mailto:William.Chong@fda.hhs.gov)

Office of combination products at [combination@fda.gov](mailto:combination@fda.gov)

**Through:** Francisco Vicenty, Chief, Respiratory, ENT, General Hospital & Ophthalmic Branch, Office of Compliance, CDRH

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**From:** LT Viky Verna, Respiratory, ENT, General Hospital & Ophthalmic Branch, Office of Compliance, CDRH

**Applicant:** Eli Lilly and Company  
1555 S Harding Lilly Corporate Center  
Indianapolis, Indiana, 46285

**Application #** BLA 125469 Dulaglutide

**Product Name:** Dulaglutide

**Consult Instructions:** To evaluate BLA 125469 submission regarding adequacy with 21 CFR part 820 requirements, to evaluate the sponsor facilities, and to provide inspectional guidance under 820.

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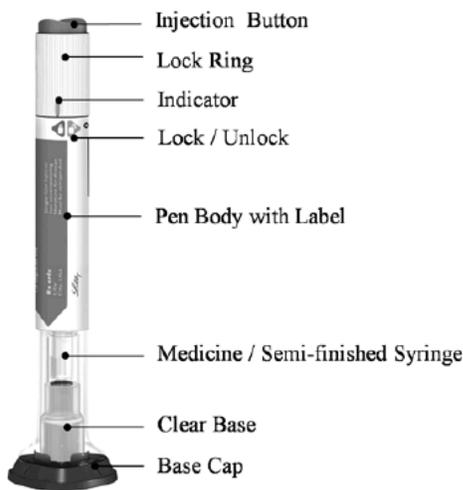
**Background**

The Office of Compliance at CDRH received a consult request from CDER/DMED for BLA 125469, Dulaglutide. The request is to assess sponsor, Eli Lilly and Company, for adequacy with 21 CFR part 820 requirements and to provide inspectional guidance for facilities.

Dulaglutide (LY2189265) is a long acting human glucagon-like peptide-1 (GLP-1) receptor agonist. Dulaglutide exhibits GLP-1 mediated effects, including glucose-dependent potentiation of insulin secretions, inhibition of glucagon secretion, delay of gastric emptying and weight loss.

The proposed indication of Dulaglutide for the U.S. is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dulaglutide drug product will be provided as a once weekly solution for subcutaneous administration.

The proposed commercial presentations of Dulaglutide will be a 1.5 mg prefilled syringe and a 1.5 mg single-use pen that has an auto-injection function. The immediate container/closure is a semi-finished (b) (4) syringe containing 0.5 mL of Dulaglutide solution which is then assembled into either the prefilled syringe or the single-use pen.

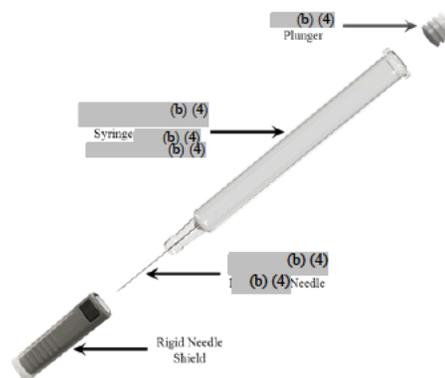


The single use pen combination product has not been previously marketed. The Lily design single use pen utilizes custom device components and the same commercially available container closure components as the prefilled syringe.

The Dulaglutide single use pen and prefilled syringe combination products consists of a device constituent part and a drug constituent part. The device constituent part is a mechanical pen injector which is a Class II medical device. The drug constituent part is the Dulaglutide in its container. The primary container closure system

for Dulaglutide injection is a (b) (4) syringe (b) (4) with an (b) (4) plunger and rigid needle shield. The syringe (b) (4) and plunger are received ready to use from the suppliers.

The container closure system components may be tested and or accepted on the basis of the Supplier's Certificate of Analysis or Certificate of Conformance (COC).



### Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following deficiencies were found:

1. There was minimal information available for review regarding compliance with 21 CFR 820.30, Design Controls as it pertains to the combination product.

### Response Review

The firm's response dated April 4, 2014 is adequate. The firm stated it followed the requirements of 21 CFR 820.30 for the development of the combination products. It explained that the design input requirements began with the creation of user need requirements created for the combination products, which are documented in a Product Requirements Document (PRD). The device/injector design input requirements are deconstructed from the PRD. All Design Outputs are defined in a Design and Development Plan and are culminated in the final review and approval of the Device Master Records for the assembled combination products and for each of the major device subsystems/constituent parts.

Design Verification and Validation were conducted and the results were previously provided for the Single-use Pen and Prefilled Syringe designs. Pre and post-market design changes made to combination products are managed through Lilly's Change Control Procedure, PDS-SOP-PDS0010 which was also provided.

- 2. Regarding compliance with 21 CFR 820.50, there was minimal information available for review pertaining to Purchasing Controls.*

#### Response Review

The firm's response dated April 4, 2014 is adequate. The firm explained that the requirements of 21 CFR 820.50, Purchasing Controls, are incorporated in the Quality System which governed the development and which will apply to the ongoing manufacturing of the single-use pen and the prefilled syringe. A listing of the firms involved in the manufacturing of the combination product and the different device components was provided.

The firm stated that its purchasing controls are established to ensure purchasing requirements are clearly specified and purchased items consistently conform to specified requirements. The firm also described the level and extent of supplier evaluation and control it exercises on its suppliers and contractors which require documented quality agreements. Lilly maintains both global quality standards (GQS), and local procedures that must align with these global quality standards.

The local Pharmaceutical Delivery Systems purchasing controls procedure PDS-SOP-0019, Purchasing Controls and Supplier Management was provided as an example. The document requires suppliers of GMP materials to notify Lilly of changes in the product so Lilly can assess and determine whether the changes have the potential to affect the quality of the finished device or combination product. Examples of agreements were provided.

- 3. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.*

#### Response Review

The firm's response dated April 4, 2014 is adequate. For its Corrective and Preventive Action (CAPA) process the firm utilizes the TrackWise Event to comply with 21 CFR

820.100. By this process, nonconformities are investigated, resolved, and assessed for effectiveness, as needed.

Lilly maintains both Global Quality Standards (GQS) and local procedures that must align with these Global Quality Standards. Lilly GQS104 Deviation Management defines its CAPA system which includes and requires:

- Identification of events, deviations, trends, and complaints requiring root-causes analysis sourced from multiple points within the quality system
- Investigation of the causes of these nonconformities
- Identification of corrective and preventive actions needed to prevent recurrence of the nonconformity
- Verification and/or validation of corrective and preventive actions to assure their effectiveness and to assure that changes do not adversely affect the device(s) involved
- Notification of those affected by the CAPA
- Reviewing of CAPA actions and metrics at the management level
- Maintaining records of each CAPA activity

The Pharmaceutical Delivery Systems CAPA procedure PDS-SOP-PDS4193, Event and CAPA Management, was provided.

CAPA management at its suppliers is addressed in the Quality Agreements between Lilly and those suppliers. Quality Agreements (b) (4) are were provided.

4. *There was no information available for review regarding compliance with 21 CFR 820.170, Installation.*

Response Review

The firm's response via e-mail dated February 17, 2014 is adequate. The firm confirmed that installation and servicing do not apply to its injectors.

5. *There was no information available for review regarding compliance with 21 CFR 820.200, Servicing.*

Response Review

The firm's response via e-mail dated February 17, 2014 is adequate. The firm confirmed that installation and servicing do not apply to its injectors.

This application was deficient overall. Additional information is required for an adequate desk review.

**Regulatory history evaluation**

After reviewing the application, the following facilities were identified as being subject to applicable Medical Device Regulations under 21 CFR part 820:

1. Eli Lilly and Company  
1555 S. Harding Lilly Corporate Center  
Indianapolis, IN 46285  
USA  
FEI Number 1819470

An analysis of the firm's inspection history over the past two years showed that a medical device inspection was conducted August 09 – 23, 2011 at Eli Lilly and Company, 1555 S. Harding/Lilly Corporate Center, Indianapolis, Indiana, 46285, USA, (FEI:1819470). This was an abbreviated GMP inspection of a tier 1 drug and class II medical device manufacturer. The firm had not been previously inspected under the medical device manufacturing compliance program.

Lilly Indianapolis serves as the manufacturing/assembly site [REDACTED] (b) (4). Primary QSIT subsystems were covered during the inspection: Design Control, Production and Process Controls, CAPA and Management Controls. Review of the EIR noted that observations were described relating to issues discovered during the pharmaceutical portion of the inspection and no objectionable conditions were noted as part of the drug/device combination product within Lilly's Indianapolis Device Manufacturing (IDM) and Delivery Device Assembly Operations (DDAO). The most recent medical device inspection at Eli Lilly and Company, 1555 S. Harding/Lilly Corporate Center, Indianapolis, Indiana, 46285, USA, is currently in progress. A review of the inspectional findings will be completed by CDRH/OC.

2. [REDACTED] (b) (4)  
[REDACTED]  
FEI Number [REDACTED] (b) (4)

An initial CDRH recommended medical device inspection, related to BLA [REDACTED] (b) (4) for [REDACTED] (b) (4), was conducted [REDACTED] (b) (4) at [REDACTED] (b) (4) (FEI [REDACTED] (b) (4)).

The inspection, for [REDACTED] (b) (4) [REDACTED] inspection that covered CAPA, Design, Management and Production and Process Controls QSIT subsystems. There was no FDA-483 issued for the medical device inspection by the investigator, however CDRH/OC converted two of the three discussion items to observations and classified the inspection as VAI.

The two observations included: 1) failure to establish and maintain procedures for identifying actions needed to correct and prevent nonconforming products and 2) failure to establish and maintain written procedures to assure correct labels, labeling, and packaging materials are used for drug products, such as written procedures shall be

followed. CDRH/OC recommended that CDER/OC inform the sponsor of the observations and the VAI classification of the facility medical device inspection.

**CDRH Office of Compliance Recommendation**

The Office of Compliance at CDRH has completed the evaluation of Application BLA 125469.

The results of the most recent inspections performed at the recommended facilities were acceptable. The firm's responses to the submission deficiencies pertaining to the Quality System Regulations were adequate. Therefore, CDRH/OC supports the approval of Application BLA 125469.

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LT Viky Verna, MSBME, MSPharm

Prepared: VVerna: 05/08/2014  
Reviewed:

CTS No.: ICC1300559  
BLA 125469

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/s/  
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ABOLADE ADEOLU

06/17/2014

Administratively checked into DARRTS by Project Manager on behalf of the reviewer

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**CLINICAL INSPECTION SUMMARY**

**DATE:** June 6, 2014

**TO:** Suchitra Balakrishnan, M.D., Ph.D., Clinical Reviewer  
Ali Mohamadi, M.D., Team Leader  
Bola Adeolu, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**FROM:** Cynthia F. Kleppinger, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**BLA:** 125469

**APPLICANT:** Eli Lilly and Company

**DRUG:** Dulaglutide (LY2189265)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATIONS:** Improved glycemic control in Type 2 Diabetes Mellitus

CONSULTATION REQUEST DATE: November 7, 2013

CLINICAL INSPECTION SUMMARY GOAL DATE: May 30, 2014 *Extended to June 9*

DIVISION ACTION GOAL DATE: September 18, 2014

PDUFA DATE: September 18, 2014

## I. BACKGROUND

Eli Lilly and Company is seeking approval of dulaglutide ((b) (4)™ is the proposed trade name) for improved glycemic control in adults with type 2 diabetes mellitus (T2DM). The application is based on the results of five pivotal Phase 3 studies.

- **H9X-MC-GBDA** A Randomized, Placebo-Controlled Comparison of the Effects of Two Doses of LY2189265 or Exenatide on Glycemic Control in Patients with Type 2 Diabetes on Stable Doses of Metformin and Pioglitazone (AWARD-1: Assessment of Weekly AdministRation of LY2189265 in Diabetes-1)

This multicenter study was conducted at 99 sites in three countries (US, Mexico and Argentina) in which the combination of metformin, pioglitazone, and exenatide was approved for use in patients with type 2 diabetes. There were 2129 subjects screened, 978 subjects randomized, and 899 subjects completed the 26-week initial treatment period. A total of 857 patients completed 52 weeks of treatment. The first patient was enrolled February 8, 2010 and the last patient completed the study May 11, 2012.

- **H9X-MC-GBDB** A Randomized, Open-Label, Parallel-Arm, Noninferiority Comparison of the Effects of 2 Doses of LY2189265 and Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes on Stable Doses of Metformin and Glimepiride (AWARD-2: Assessment of Weekly AdministRation of LY2189265 in Diabetes-2)

This multicenter study was conducted at 87 study centers in 20 countries. There were 1300 patients screened, 810 patients randomized, 807 had at least one dose of study drug, and 723 patients completed the study. The date the first patient was randomized was May 5, 2010 and the last patient completed the study November 23, 2012.

- **H9X-MC-GBCF** A Phase 2/3, Placebo-Controlled, Efficacy and Safety Study of Once-Weekly, Subcutaneous LY2189265 Compared to Sitagliptin in Patients with Type 2 Diabetes Mellitus on Metformin

This multicenter study included 111 study centers in 12 countries. There were 2195 patients screened, 1471 patients that entered the lead-in period, 1202 patients that were randomized (230 patients during Stage 1 and 972 patients during Stage 2) and 831 patients that completed the 12-month endpoint. The first subject visit occurred August 27, 2008 and the last subject completed July 6, 2012.

- **H9X-MC-GBDC** The Impact of LY2189265 versus Metformin on Glycemic Control in Early Type 2 Diabetes Mellitus (AWARD-3: Assessment of Weekly AministRation of LY2189265 in Diabetes-3)

This multicenter study was conducted at 101 study sites in 19 countries. There were 1396 patients screened, 807 patients randomized, 701 patients completed 26-weeks treatment and 651 patients completed 52-weeks treatment. There were 409 patients that participated in the optional Test Meal Addendum. The first patient enrolled May 24, 2010 and the last patient completed June 19, 2012.

- **H9X-MC-GBDD** The Impact of LY2189265 versus Insulin Glargine Both in Combination with Insulin Lispro for the Treatment to Target of Type 2 Diabetes Mellitus (AWARD-4: Assessment of Weekly AministRation of LY2189265 in Diabetes - 4)

This multicenter study was conducted at 105 study centers in 16 countries. There were 1256 patients screened, 884 patients randomized, 759 completed 26 weeks and 719 completed 52 weeks. The first patient enrolled October 27, 2010 and the last patient completed September 21, 2012.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of BLA 125469 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

## II. RESULTS (by Site):

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Preliminary Classification
Oswaldo Brusco Site #15	H9X-MC-GBDA 8 subjects	2/19- 3/3/2014	VAI
Guillermo Umpierrez Site #10  Site #136	H9X-MC-GBCF 17 subjects  H9X-MC-GBDC 11 subjects	1/28- 2/24/2014	NAI
Jonathan K Wise Site #46  Site #17	H9X-MC-GBCF 9 subjects  H9X-MC-GBDD 20 subjects	1/21- 2/5/2014 (Eight days onsite. Inspection interrupted due to	VAI

		hazardous weather)	
Alan Wynne Site #6	H9X-MC-GBDD 14 subjects	3/4 – 3/26/2014	VAI
Site #90	H9X-MC-GBDA 25 subjects		
Site #3	H9X-MC-GBCF 8 subjects		
Cecilia Luquez Site #3	H9X-MC GBDB 30 subjects	3/10- 3/14/2014	VAI
Federico Perez Manghi Site #201	H9X-MC-GBDC 26 subjects	2/18- 2/28/2014	NAI
Site #106	H9X-MC-GBDD 39 subjects		
Jorge Waitman Site #6	H9X-MC-GBDB 38 subjects	3/3- 3/7/2014	NAI
Eli Lilly and Company	All studies	4/23-25, 28- 30, 5/1-2, 5- 8, 5/19/2014	NAI

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

**NOTE:** For all studies, the sponsor communicated in the BIMO section of the application that they do not collect data on all inclusion and exclusion criteria. On the case report forms, sites indicate the reason for screen failure as “sponsor decision”, “physician decision”, “subject decision”, “adverse event”, or entry “criteria not met”. If entry criteria are not met, sites indicate one criterion that was not met, although it may not be the only criterion.

One site for study **H9X-MC-GBCF** had been inspected previously as a for-cause inspection.

- **Site 044 (Clarita Ketels, St Clair Shores, MI)**

The Office of Scientific Investigations (OSI) directed a for-cause inspection of Dr. Ketels’ site in December 2011 after receiving a complaint which alleged inappropriate good clinical practice (GCP) conduct and then a subsequent site closure notification by a different sponsor who alleged lack of principal investigator oversight. The inspection focused on four protocols, including H9X-MC-GBCF. The final classification of the

inspection was VAI. The evidence did not show significant subject safety or data integrity issues.

During the sponsor monitoring of this site, concerns were raised regarding high turnover of site personnel which contributed to training issues, quality concerns, and GCP noncompliance. The site randomized three patients in this study until termination. Data for the three patients enrolled at Site 044 remained in analysis datasets for purposes of analysis and reporting. No other serious quality problem was observed during the conduct of the trial.

**1. Osvaldo Brusco, M.D.**

5814 Esplanade Dr.

Corpus Christi, TX 78414-4173\*

\*This is a new location as of May 2013

- a. What was inspected:** The inspection focused on informed consent documents (ICDs), Institutional Review Board (IRB) correspondence, Form FDA 1572, financial disclosures, curriculum vitae, delegation forms, site training records, monitoring reports, inclusion/exclusion criteria checklist, enrollment logs, subject source documents including medical history records, electronic case report forms (eCRFs), subject diary logs, drug accountability/disposition records, drug temperature logs, concomitant medication records, and adverse event reports. There were eight enrolled subject records fully reviewed. The records of five screen failures were also reviewed.
- b. General observations/commentary:** There were 16 subjects screened at the site, eight subjects enrolled, and six completed the study. The IRB of record was (b) (4). The approved Spanish translated informed consent was not used (not needed). All approvals and all financial disclosure forms were in order. Training was provided by the sponsor through (b) (4). All subjects were consented before receiving trial procedures and medication. There were no serious adverse events (SAEs) at the site. It was noted that research records were not sufficiently secured with limited access by research staff as the records were on shelves in the workstations exposed to the subjects.

For the eight enrolled subjects, all had an HbA1c measurement at Visit 4 prior to randomization. The policy of the contract research organization that monitored the site was to have available past medical records for five years at the site. However, past medical records were not all at the site; verbal history was obtained. The primary efficacy endpoint was verifiable. There were several adverse events (AEs) such as cellulitis, sore throat, cold with runny nose plus sneezing documented by subjects in their study diaries but not transcribed to the AE logs and eCRFs.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued for the following deficiencies:

**OBSERVATION 1**

Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests.

The site received a new version of the ICD approved by the IRB on 9/28/2011. It contained new safety wording regarding bladder cancer for the licensed drug pioglitazone. Five subjects were re-consented late (i.e. not within the 14-day window requested by the sponsor).

Subject	Initial Contact	Visit Date Following ICD Revision	Re-consent Date	Days*
706	10/21/11	10/13/11 (V-LV30)	10/13/11(V-LV30)	15
707	10/18/11	10/20/11 (V-12)	10/20/11(V-12)	22
712	10/21/11	10/3/11 (V-11)	1/19/12 (V-12)	98
714	10/21/11	11/11/11(V-10)	1/4/12 (V-11)	112
715	10/21/11	10/3/11(V-10)	1/18/12(unscheduled)	113
*Days from the revised ICD.				

*OSI Reviewer Comment: In Dr. Brusco's written response, he acknowledged that the aforementioned subjects were re-consented beyond the 14 days required by the sponsor. He indicated that subjects were contacted for re-consent, but subjects were unable to return to the site on time. Site documented phone calls to subjects requesting re-consent. All ICDs for the main study were properly signed. As a corrective and preventive action plan, the study coordinator has been re-trained on the importance of following key sponsor communications that require prompt action. In addition, the site will create a re-consent tracking log. Response is acceptable.*

**OBSERVATION 2**

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

1. Site enrolled two subjects who did not meet eligibility criteria. Specifically, protocol exclusion criterion #16: history of edema or fluid retention, or any of the following CV conditions within 2 months of Visit 1: congestive heart failure Class II, III, or IV, acute myocardial infarction, or cerebrovascular accident. Subject 706 and Subject 708 were reported to have a medical history of pre-existing lower extremity edema. Specifically Subject 706 was reported to have left lower extremity trace edema at Visit 1 on 6/10/10. Medical records indicated edema started 5/29/09. Subject 706 was randomized on 9/15/10 (Visit 5). For Subject 708, lower extremity edema was reported at Visit 1 (6/23/10) and was noted to be on treatment for edema. Despite past medical history of edema, Subject 708 was randomized at Visit 5 (8/18/10).

*OSI Reviewer Comment:* In his response, Dr. Brusco said that under his clinical judgment, both subjects had only bilateral lower extremity trace edema and that such a small amount can be subjective. For Subject 708, he attributed the trace edema to 1) subject was on amlodipine (combined with benazepril), well known to cause lower extremity edema, and 2) subject was on Actos 45 mg and had gout. It was determined that the edema was not cardiovascular in nature (by normal physical exam and no personal history of this condition). For Subject 706, cause of the bilateral trace lower extremity edema was unknown; there was no history of cardiovascular disease. Response is acceptable.

2. Site enrolled one subject who did not meet the inclusion criteria. An inclusion criterion requires that subjects have a body mass index (BMI) of 23-45 kg/m<sup>2</sup>, inclusive, to be included in the study. Specifically, prior to randomization, Subject 714 was recorded to have a BMI > 45 kg/m<sup>2</sup> during the lead in period, prior to randomization. The site measured the subject's weight as originally 129.3 kg before it was crossed out to 127.5 kg by (b) (6) with initials but no date.

*OSI Reviewer Comment:* The protocol states subjects must have a BMI between 23-45 kg/m<sup>2</sup>, inclusive, to be eligible for the study. Subject 714 calculated BMI ranged from 45.1 to 46.1 (lead-in to randomization day). Visit 1 BMI was 45.4 kg/m<sup>2</sup>. In his written response, Dr. Brusco said he rounded down any number in the range of 45.1 – 45.4 down to 45. Visit 2-3 (lead-in) and Visit 4 (lead-in/randomization) were not a part of the inclusion criteria.

*As a corrective action plan, site will request the study monitor's cell phone number to discuss, prior to or at screening visit, uncertainties in protocol wording. Dr. Brusco has re-trained the study coordinator on proper documentation practices including: 1) sign and date corrections; 2) include reason for changes in source notes; 3) all used scales (manual and digital) undergo annual calibration by an outside company (documentation is available upon request); and 4) site has incorporated, as standard policy, to request medical records that would provide all the necessary information prior to screening. Response is acceptable.*

3. Two enrolled subjects' study diaries contained adverse events that were not transcribed to case report forms (CRFs) as per the protocol. Subject 706 had diary entries of 1) Painful sore throat; swollen lymph nodes (severity severe), 2) cold with runny nose and sneezing (moderate); Subject 712 had diary entry of cellulitis (severe).

*OSI Reviewer Comment:* Reported AEs do not appear to have significant impact on subject safety. In Dr. Brusco's written response, he acknowledges that these AEs were not captured. During study visits, the site staff questioned subjects on the occurrence of AEs and subjects replied "no", even though subjects recorded AEs in their diaries. Therefore, the site and study monitor missed subject self-reported AEs. Dr. Brusco indicated in his written response that the study coordinator has

*been re-trained to thoroughly evaluate study log books with subjects, regardless of the oral history. Response is acceptable.*

4. Two enrolled subject's lab levels were not re-tested once site was notified by the laboratory to do so. Specifically, Subject 706 and 708 did not have their lipase and amylase levels recollected in a timely manner as requested by the Lab following Visit 11 (6/16/11) and Visit 5 (8/19/10), respectively.

Subjects 706 and 708 lab reports dated on 6/17/11 and 8/19/10, respectively, stated "Patient may meet discontinuation from LY2189265: Please re-test Amylase and Lipase within 24 – 72 hours and contact Eli Lilly designated personnel to discuss pancreatic monitoring. Refer to protocol discontinuation criteria from LY2189265 and Adverse Event of Interest: Acute Pancreatitis." Section 10.3.1.3 states "Further diagnostic assessment will be recommended whenever lipase and/or amylase are confirmed (based on repeated measurement) to be > 3 times the upper limit normal (ULN) at any visit after randomization (Visit 5), including asymptomatic patients."

A sponsor correspondence dated 9/12/11 indicated that "First, an elevation of lipase and/or amylase even if confirmed may not be diagnostic of pancreatitis. Further evaluation is needed, signs and symptoms, and imaging as hyperenzymemia alone is not pancreatitis or inflammation and destruction of pancreatic tissue. Second, please contact patients within a day or two for retesting when a lipase and/or amylase value is 3 times the upper limit of normal. We know it is difficult to follow our guidance of 3 to 4 days for a retest but try your best along with your study coordinator to achieve repeating testing as soon as possible."

*OSI Reviewer Comment: The protocol does not specifically state when the sites should recollect lipase/amylase levels to confirm elevated levels; however, subjects' lab reports requested that the site re-collect levels within 24-72 hours. In addition, the sponsor's correspondence referenced above was dated after subjects' lab test results. Source records indicate that site re-collected lipase and/or amylase lab levels on 8/11/11 and 9/1/10, for Subject 706 and 708, respectively. Lipase levels for Subject 706 were within normal range; however, Subject 708's lipase and amylase levels were above normal range, but not > 3 x ULN.*

<b>Subject</b>	<b>Lab Level</b>	<b>Re-test of Level</b>	<b>Reference Range</b>
706	Lipase 190 U/L (Visit 11: 6/16/11)	Lipase: 35 U/L (8/11/11)	0-60 U/L
708	Lipase 499 (Visit 5: 8/18/10)	Lipase 131 U/L (9/1/10)	
	Amylase: 429 (Visit 5: 8/18/10)	Amylase 141 U/L (9/1/10)	20-112 U/L

*In addition, following a discussion with the field investigator, the PI indicated no SAEs occurred and no signs and symptoms were observed. In Dr. Brusco's written response, he acknowledged the delay in recollection of lipase levels. Under his clinical judgment, he considered the lipase levels to be not clinically significant, based on subject's negative physical and oral exam for pancreatitis and preceding elevated baseline lipase and amylase level (Subject 708). As a corrective action plan, he has discussed the importance of following procedures for re-testing values in a timely manner with the study coordinator. Response is acceptable.*

*Although this item is clinically significant, this is not a protocol deviation because the protocol does not specifically indicate when sites should confirm elevated levels with a repeated measurement. In addition, scope and severity of this 483 item is minimal in impact. Re-tested levels were less than 3 x ULN. Response is acceptable.*

There were also issues discussed verbally with the PI and staff at the close-out meeting.

- Physical exam (PE) for one (#706) enrolled subject was not conducted at Visit 5 (9/15/10) as required by the protocol; instead the site conducted the PE at an unscheduled visit on 10/14/10. Specifically, the protocol requires that PE be conducted at Visits 5, 12 and end of treatment.
- ECGs were not obtained from one (#700) enrolled subject at Visit 10 (12/17/10). Specifically, the protocol required that ECGs be collected at Visits 1, 5, 10, 12 and end of treatment. The site did assess ECGs at Visit 12, which is the next required ECG collection visit. (The site was missing all Visit 12 source documents, but the site was able to request Visit 12's ECGs from sponsor). In addition, the site did not collect health outcome scale/questionnaires at Visit 10 as per the protocol. Source documents indicated that health outcome forms were not filled out by the subject due to site error. This was the only occurrence of missed questionnaires.
- Site recorded one (#707) enrolled subject's answers to health outcome questionnaires and had subject initial and date the source document (plain white paper). The protocol states "...questionnaires will be completed by the patients at specific clinics according to the study schedule." The protocol does not state that subjects are required to fill questionnaires in their own handwriting.
- Site incorrectly dated several informed consent documents in the format of MMDDYY, instead of the correct DDMMYY as stated on the forms.
- PI did not check that the study was Phase 2 or 3 in Section 8 of an updated signed Form FDA 1572 dated 12/7/09.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above,

they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

**2. Guillermo E. Umpierrez, M.D.**

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**a. What was inspected:** The inspection covered IRB approvals and correspondence, subject selection criteria, 100 % informed consents, study drug accountability, source data verification, FDA 1572s, financial disclosure forms, training, delegation of duties, and monitoring. For study H9X-MC-GBCF, eight subject files were reviewed. For study H9X-MC-GBCF, eight subject records were reviewed. For study H9X-MC-GBDC, seven subject records were reviewed.

**b. General observations/commentary:** For study H9X-MC-GBCF, 35 subjects were screened and 17 subjects were randomized. The first subject was screened on 11/20/2008. For study H9X-MC-GBDC, 16 subjects were screened and 11 subjects were randomized. The first subject was screened on 8/13/2010. The PI maintained adequate oversight of the studies at his site. All records were organized and complete. (b) (4) was the IRB of record. There were no major deficiencies with the recording of source data and the primary efficacy endpoint was verifiable. There was no evidence of underreporting of adverse events and all serious adverse events were reported as required per the IRB and protocol. There were no discrepancies found between the investigational product log and the source documents. There was no master investigational product accountability log, only subject's individual investigational drug accountability log. One page of Subject 3614's lab report was missing, but the site was able to receive a duplicate copy from the laboratory.

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

**c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**3. Jonathan K Wise, M.D.**

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**a. What was inspected:** The inspection focused on informed consent documents

(ICDs), Institutional Review Board (IRB) correspondence, Form FDA 1572, financial disclosures, curriculum vitae, delegation forms, monitoring reports, inclusion/exclusion criteria checklist, enrollment logs, subject source documents including medical history records, subject diary logs, drug accountability, concomitant medication records, and adverse event reports. For study H9X-MC-GBCF, the nine randomized subjects' records were reviewed. For study H9X-MC-GBDD, 10 subjects' records were reviewed.

- b. **General observations/commentary:** For study H9X-MC-GBCF, 25 subjects were screened, 11 subjects enrolled but two withdrew consent prior to Visit 4 randomization so nine subjects were randomized. All enrolled subjects appear to have met eligibility criteria.

For study H9X-MC-GBDD, there were 27 subjects screened and 20 subjects were randomized.

- Subject 907 should have been discontinued from the study prior to randomization. Blood glucose levels included in the subject's diary between Visits 3 and 4 indicate glycemic control and, therefore, the subject should have been discontinued at Visit 4 as per the protocol. The subject was randomized on 4/21/11 and completed the study on 6/12/12. (It should be noted that blood glucose measurements before Visit 3 and after Visit 4 recorded in the subject's diary include some values outside of the guidelines for glycemic control).
- Subject 901 did not have a stabilization period between Visit 2 and Visit 4 of at least seven weeks as per protocol. Oral antihyperglycemic medication (OAM) Amaryl 8mg was stopped on 11/30/10. The subject was randomized on 12/16/10. This deviation was reported to the Sponsor and IRB and the subject allowed to continue in the study (Sponsor approval)
- Subject 910 did not have a stabilization period between Visit 2 and Visit 4 of at least seven weeks as per protocol. The subject discontinued OAM (Januvia and Amaryl) on 3/15/11 at Visit 2 and the subject was randomized on 4/13/11 at Visit 4.

For both studies audited, there were no informed consent issues. No lapses in IRB approvals or failure to file required reports were noted. Financial disclosure forms were reviewed and no conflicts were noted. Records were noted to be legible and organized. Dr. Wise's handwritten signature appears throughout study source documents indicating his performance of physical examinations and his verification that all medical information is accurate and complete for each study visit. His signature is also present on source documents signifying his review of EKG tracings, laboratory reports, and adverse event forms. Efficacy endpoints were verifiable.

There was definite underreporting of adverse events, pre-existing conditions, and concomitant medications.

For study H9X-MC-GBCF:

- Subject 2357: Pre-existing acid reflux (in source, not reported on CRF)
- Subject 2359: Pre-existing hypercholesteremia (in source, not reported on CRF); concomitant medication associated with reported SAE hospitalization (Rocephin in source, not reported on CRF)
- Subject 2367: Pre-existing hypercholesteremia (in source, not reported on CRF)
- Subject 2371: Unscheduled EKG performed on 8/17/10, however no symptoms (i.e. chest pains, shortness of breath) were recorded in CRFs as AEs

For study H9X-MC-GBDD:

- Subject 900: Baseline Visit 4 (12/16/10) CPK value was 175 IU/L and microalbumin/creatinine Ratio value was 19 mg/g. At Visit 13 (12/19/11) CPK value was 772 IU/L and microalbumin/creatinine ratio was 3126 mg/g.
- Subject 901: Two hypoglycemic events reported in subject diary on 2/11/11 and 2/17/11; reported in CRF but then deleted
- Subject 907: Baseline laboratory values indicative of hypercholesteremia. Lipid levels remained high throughout the study.
- Subject 916: Recorded in the subject's diary on 2/20/12, "start HCG," with no further explanation as to why it was started. Also recorded in the diary on 12/12/11 "next 3 days higher because of cortisone shot and pills for stomach/rib pain" was scratched out but readable, without clarification.
- Subject 922: Increased microalbumin/creatinine ratio baseline value on 8/2/11 of 2916 mg/g; value at Visit 13 on 7/16/12 was 4430 mg/g.
- Subject 925: One hypoglycemic event recorded in the subject dairy on 9/10/11, unreported in CRF
- Subject 925: Augmentin use was recorded in the subject's diary for dates 9/7-17/11; however, this medication was not reported in the CRF nor was an associated adverse event recorded for which the medication was taken

These studies were conducted during the same time period as the last March 2012 FDA inspection for another study. That inspection revealed underreporting of AEs, concomitant medications, and hypoglycemic events contained in subject diaries. The site has changed their practices to prevent further deficiencies. Corrective actions included a new standard of practice consisting of a double-check system to ensure all adverse events and concomitant medications are entered into case report forms (CRFs), the creation of a Master Adverse Event Log for each study with monthly reviews by Dr. Wise, performing a more detailed baseline review of systems to ensure the completeness and accuracy of each subject's medical history, and educating each subject on the reporting of adverse events at each visit.

Since the deficiencies observed in the two audited studies were identical to the

deficiencies cited during the March 2012 FDA inspection and the audited studies were conducted in the same time period as the studies audited in the 2012 inspection, an FDA 483 was not issued by the FDA field investigator. Although no FDA 483 was issued at the conclusion of the inspection, the observations were discussed with Dr. Wise. Initial field classification was No Action Indicated (NAI). After review of the Establishment Inspection Report, the classification was upgraded to Voluntary Action Indicted (VAI). Although changes at the site had been instituted, there was substantial underreporting of adverse events, pre-existing conditions, and concomitant medications found with the conduct of both studies and the classification reflects that deficiencies were found.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although deviations were noted as discussed above and there were several isolated adverse events not reported, the audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

**4. Alan G. Wynne, M.D.**  
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Topeka, KS 66606\*

\*FMD-145 correspondence should be addressed to:

Alan G. Wynne, M.D., Cotton-O'Neil Clinical Research Center, c/o Mary J. Martell, Director, 823 SW Mulvane St., Suite 240, Topeka, KS, 66606.

- a. **What was inspected:** For Study H9X-MC-GBCF, there were 18 subject records reviewed. For Study H9X-MC-GBDA, there were 36 subject records reviewed. For Study H9X-MC-GBDD, 19 subject records were reviewed. IRB approvals and communications, sponsor communications, delegation of studies, and staff qualifications were reviewed. Due to the large volume of data from the three trials, the focus was on protocol compliance, adverse events and data integrity with comparison of source documents to line listings submitted by the sponsor to the application.
- b. **General observations/commentary:** For Study H9X-MC-GBCF, 18 subjects were screened and 8 subjects were randomized. Original IRB approval for the conduction of this study was granted on 6/6/08. For Study H9X-MC-GBDA, there were 36 subjects screened and 25 subjects randomized. Original IRB approval for the conduction of this study was granted on 11/25/09. For Study H9X-MC-GBDD, there were 19 subjects screened and 14 subjects randomized. Original IRB approval for the conduction of this study was granted on 5/20/10.

The inspectional site, known as the Cotton-O'Neil Diabetes and Endocrinology Center, is one of several ambulatory clinics, collectively known as the Cotton-O'Neil Clinical Research Center. This research center is a division of Stormont-

Vail Healthcare, which also includes Stormont -Vail Regional Health Center Hospital. A Central IRB, [REDACTED] (b) (4) was used.

All three studies lacked some required documentation in regards to nurses' notes, notes to files and general documentation which would have allowed the ability to review the details and chronology of occurrences during the study. This was especially in regards to study H9X-MC-GBDD. The sponsor for the study did not provide forms which require the firm to document the date of discovery for SAEs.

During the inspection of Dr. Wynne, there were three instances (Subjects 4469, 4478, and 4479) in Study H9X-MC-GBDA in which he rescue dosed subjects outside of the protocol (earlier than permitted per protocol and/or without the required qualifying HbA1c performance). He received protocol waivers from the Sponsor.

At the end of the inspection, a Form FDA 483 was issued for the following:

#### **OBSERVATION 1**

An investigation was not conducted in accordance with the investigational plan. Specifically,

- 1) Failure to report, within 24 hours of awareness, as required per protocol H9X-MC-GBDD, the following Serious Adverse Events (SAEs):
  - a) Hospitalization and surgery of Subject 356 on [REDACTED] (b) (6)
  - b) Hospitalization and surgery of Subject 356 on [REDACTED] (b) (6)

Although documentation was available in the subject chart, both SAEs were not reported until October 13, 2011 during a sponsor-monitoring visit.

*OSI Reviewer Comment:* Subject 356 was hospitalized on both [REDACTED] (b) (6) [REDACTED] due to surgical repair of right and left rotator cuffs. Subject records document site knowledge of the [REDACTED] (b) (6) hospitalization on or before 10/3/11. The earlier dated hospitalization [REDACTED] (b) (6) was discovered on 10/12/11. Neither of these hospitalizations was reported as required per protocol. Events were assessed as not drug related.

*Dr. Wynne responded that the events were initially considered AEs. He will revise the standard source document worksheet for logging adverse events to include a column that will prompt the evaluation of SAE criteria. This will be implemented by June 2, 2014 and will apply to all trials going forward. Staff will also be trained.*

- 2) Per SOP entitled, "Clinical Trial Interactive Voice Response System IVRS (IVRS) User Guide - User Instructions – US H9X-MC-GBDD 15

-Nov-2007", all subject visits between 1 and 14 for Study H9X-MC-GBDD required phone calls from the study site to the IVRS to provide information for data collection and for receipt of study conduction instructions, to include study drug assignment. The site failed to perform 49 of 290 required IVRS phone calls during the conduction of this study.

*OSI Reviewer Comment: The IVRS in clinical trials is utilized for randomization, and dissemination and collection of subject data throughout the conduction of a clinical trial. The IVRS required by the sponsor involved the use of recorded instructions for each subject. Each of at least 14 prescheduled subject visits required the staff member to place a call to the IVRS to provide data and/or receive the recorded instructions. On many occasions the IVRS provided recorded instructions on the distribution of study medication to the subject. There were 49 calls not performed but there is no documentation of significance.*

*Dr. Wynne responded that the total uncompleted and/or untimely IVRS phone calls are 40, which include calls that were originally placed on the visit date, but not "closed," in addition to calls that were conducted late. All IVRS calls were conducted prior to the next visit date. The Clinical Research Center will revise the standard source documentation worksheet for protocol visit procedures to include documentation of conducting the protocol-specific IVRS requirements. This will be implemented by June 2, 2014 and will apply to all trials going forward. Staff will also be trained.*

- 3) Per protocol, participants of study H9X-MC-GBDA were only to be provided rescue therapy/therapeutic intervention under specified guidelines. Protocol specifications were not adhered to in the following instances:
  - a) Although protocol H9X-MC-GBDA lists the requirement of "HbA1c values  $\geq$  8% (on two or more occasions at least 12 weeks apart) during the second 26 weeks of the treatment period" for consideration of further therapeutic intervention, study Subject 4469 and Subject 4479 were provided therapeutic intervention without the performance and assessment of the required HbA1c testing.
    - o *Subject 4469 was prescribed rescue therapy in the form of insulin on 6/28/11, based on results of one HbA1c lab value measured on Visit 10/Week 26 dated 5/3/11. This was the subject's final visit of the first 26 week treatment period. The protocol required the subject to have begun the second 26 week treatment period and have two HbA1c tests with qualifying results, evaluated 12 weeks apart during this period in order to receive rescue therapy. The subject was prescribed rescue therapy without assessment of an*

- additional HbA1c measurement as required per protocol.*
- *Subject 4479 was prescribed rescue therapy without the assessment of either of the protocol required HbA1c assessments. Subject 4479 attended the scheduled, Visit 10/Week 26 visit on 7/1/11. It was during this visit that the subject was prescribed rescue therapy in the form of insulin.*
- b) Although, protocol H9X-MC-GBDA lists the requirement of "HbA1c values  $\geq$  8% (on two or more occasions at least 12 weeks apart) during the second 26 weeks of the treatment period", for consideration of further therapeutic intervention, study Subject 4478 was provided therapeutic intervention without the performance and assessment of all required HbA1c testing.
- *Subject 4478 did not have two HbA1c values qualifying the subject for rescue therapy per protocol. One HbA1c value of 8.3 assessed on October 3, 2011 was collected during the second 26th week period. There was no other qualifying HbA1c testing performed during this protocol specified period.*

*OSI Reviewer Comment: For Subjects 4469 and 4479, Dr. Wynne disagreed with the observation and responded "Upon inquiring with the sponsor protocol medical monitor, we were notified on 20May2011 '....visit 10 is at 26 weeks and we can consider this after 26 weeks for protocol.' The protocol provided "investigator discretion" concerning rescue interventions, and the sponsor emailed approval.*

*For Subject 4478, Dr. Wynne acknowledged this observation. He determined this was required to meet the medical safety needs of the subject. In his response, there will be training for investigators concerning protocol compliance and rescue plans, including thorough documentation of the decision-making process for initiating rescue therapy, sponsor communications, and other applicable processes.*

- 4) During the conduct of study H9X-MC-GBDD, the PI failed to ensure study participants assigned to specified study drug treatment arms performed first dose injection under the supervision of the study team at Visit 4, as required by the protocol. Subject 365 was permitted to transport study medication away from the study site and inject the initial study dose without the observation and supervision of study staff.

*OSI Reviewer Comment: New procedures are being developed by the site to avoid any further incidence as noted above. For all protocols involving an investigational product that is to be administered at the research site, an investigator will sign-off on of the conduct of the visit prior to the subject's*

*departure from the research site. This will be implemented by June 2, 2014 in order to provide adequate time to develop a system and to train staff. It will apply to all trials that open after the implementation date.*

## **OBSERVATION 2**

Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically, during the conduction of studies, H9X-MC-GBDD, H9X-MC-GBDA and H9X-MC-GBCF, the PI failed to prepare and maintain adequate and accurate subject case histories which provide documentation of deviations from protocol and chronological timelines of all occurrences related to the conduct of these studies.

*OSI Reviewer Comment: The FDA field investigator made several requests for documentation during the review of the three studies. A system of "notes to file" was not established for the studies to account for and explain discrepancies or work not performed. Subject charts had some details documented, not as progress notes, but as small notes on various pages established for purposes other than recording incidents or discrepancies. Several details requested were "jotted down" as notes in various areas, within the subject records without the ability to create true chronology or timelines.*

*In his written response, the revised SOP for source documentation will contain the following language:*

*"All subject case histories are to be established following the principle of ALCOA, ensuring that the information is attributable, legible, contemporaneous, original and accurate." In addition, clinical research coordinator documentation will be contributed to source documentation in a system that clearly demonstrates the chronological timeline".*

*A study-specific, site generated deviation log will be maintained separately from the sponsor generated deviation log. The site log will describe all activities considered to be deviations and the corresponding supporting documentation. This will be implemented by June 2, 2014 in order to provide adequate time to develop a system and to train staff. It will apply to all trials that open after the implementation date.*

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although deviations were noted as discussed above, they span all three studies and the audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

**5. Cecilia Luquez, M.D.**  
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Cordoba, Cordoba 5006  
Argentina

- a. **What was inspected:** Records reviewed included ethic review committee (EC) approvals, CVs, training, monitoring reports, site signature and responsibility logs, site training logs, and drug accountability records. The initial informed consent form (ICF) documents for all randomized subjects were reviewed. The re-consenting of subjects during the trial was reviewed for three randomized subjects. For three subjects, the inclusion/exclusion criteria, adverse event/serious adverse events, prior history, prior medications, contaminant medications, HbA1c values and protocol deviations records were reviewed. For an additional 10 subjects, sponsor data tables were verified for all HbA1c primary endpoints, to verify adverse event reporting and to verify concomitant medications taken while on study drug. The reason for subject withdrawals and SAE reporting were also audited against the sponsor data table for affected subjects. The receiving documents for approximately 10 shipment records were reviewed and verified that the receipt dates, quantity received and the condition of the shipment were documented properly.
- b. **General observations/commentary:** The site screened 50 subjects. Thirty (30) subjects were randomized. The first subject (Subject 100) was screened on August 27, 2010 and was subsequently randomized on October 14, 2010. The last subject to have a study follow-up visit was identified as Subject 141 on November 15, 2012. Per Argentina regulations, the study initially had to be reviewed and approved by both the national and local ethics review committees. In addition, once approved the protocol and ICF was registered with the Ministry of Health (MOH). Subsequent changes to the protocol or Informed Consent Form (ICF), if considered substantial, also had to be approved by both the local and national ethics review committees. In March 2011, the regulation changed and the national committee was not necessary. After that date only local approval was necessary. The site still had to register the approved changes with the Ministry of Health before implementing the changes.

The clinical investigator followed the protocol approved by the EC in terms of subject selection, randomization scheme, required evaluations, administration of the test article, and frequency of follow-up. The informed consent used included the eight required elements in 21 CFR 50.25(a). The site had financial disclosures on file for the Principal Investigator and the sub-investigators that were signed and dated on July 6, 2010 prior to study screening. No financial interests were identified.

Source documentation was paper based. The data recorded in the clinic charts was later transferred to the electronic data base by the PI or sub-investigator. The site maintained documentation of subject visits and communications in their clinic medical chart. Subject source documents were organized,

maintained, legible and complete. The primary efficacy endpoint was verifiable. SAE's audited indicated that they were reported to the sponsor within 24 hours.

The assignment requested that it be verified that the patients were taking the maximum tolerated doses for the oral medications metformin and glimepiride, but not higher than the maximum approved doses. The maximum dose allowed per the Argentina labeling of the drugs is as follows:

Metformin 850 mg tablet – Maximum labeled dosage 2550 mg/day  
Metformin 1000 mg tablet – Maximum labeled dosage 3000 mg/day  
Glimepiride 4 mg tablets – Maximum labeled dosage 8 mg/day

For Subject 106, Subject 114 and Subject 141 records indicated that all three subjects were taking Metformin 2550 mg/day and Glimepiride 8 mg/day at Visit 3 and Visit 4 during the run-in period. None of the subject records were found to be exceeding the maximum dosages.

The inspection found that all adverse events and concomitant medications were not reported per the protocol requirements.

At the end of the inspection, a Form FDA 483 was issued for the following:

#### **OBSERVATION 1**

An investigation was not conducted in accordance with the investigational plan.

Specifically,

A. Approximately 4 of 10 subject source records reviewed included adverse events or prior medical history that was not reported into the electronic database. For example:

- 1) Subject 146 did not have adverse events of gastritis, sinusitis or three episodes of bronchitis reported.
- 2) Subject 119 did not have an adverse event of gastritis reported.
- 3) Subject 137 did not have an adverse event of bronchitis reported.
- 4) Subject 114 did not have a prior history of headaches reported.

B. Approximately 4 of 10 subject source records reviewed included concomitant medications that were not reported into the electronic database. For example:

- 1) Subject 146 did not have antibiotic concomitant medications reported on four occasions (Amoxicillin, Decidex, Amoxicillin, Clarithromycin)
- 2) Subject 137 did not have aspirin, Loratadine (Loratine) or Betametasone (Betamethasone) concomitant medications reported.
- 3) Subject 114 did not have Migral concomitant medication reported (*The*

*site indicated that Migral was a combination drug of ergotamine, caffeine and dipyrrone available in Argentina for the treatment of migraines)*

- 4) Subject 141 did not have atorvastatin concomitant medication reported.

There was also discussion at the close out meeting regarding protocol deviations. It was also noted that approximately 4 of 11 protocol violations identified in the sponsor data table describing non-compliance with study drug treatment were entered in error. The sponsor data table identified 11 subjects as have treatment compliance < 75% for the specified visits. However, during record review for one of the subjects it was noted that source data indicated good treatment compliance. The Clinical Investigator and the Sub-Investigators reviewed the information in the clinic chart and diaries for this subject and for the other subjects identified on the sponsor's data table. They also reviewed the electronic data base to see if the non-compliance was entered in error. Dr. Luquez indicated that the information appeared to be a typo for four subjects.

- Subject 102 – The sponsor's data table indicates that this subject had treatment compliance less than 75% at Visit 8. Review of the clinic chart for Visit 8, which was conducted on December 16, 2010, indicated that drug compliance was 100%. Clinic chart notes for Visit 9 also indicate 100% compliance. Review of the subject diary for the time period of October 29, 2010 – January 14, 2011 indicates no problem with study drug compliance.
- Subject 108 – The sponsor's data table indicates that this subject had treatment compliance less than 75% at Visit 7. Review of the clinic chart for Visit 7 indicated that drug compliance was 100%. Review of the subject diaries from November 24, 2010 – April 13, 2011 also demonstrated good study drug compliance.
- Subject 111 – The sponsor's data table indicates that this subject had treatment compliance less than 75% at Visit 7. Review of the clinic chart documents a telephone call to the subject on December 22, 2010 reporting 100% compliance. For Visit 7, which was conducted on December 27, 2010, the site did not document any problems with drug compliance. Telephone contact on January 10, 2011 indicated good compliance with study drug. The clinic chart for Visit 8, conducted on January 21, 2011 also indicates 100% compliance with study drug. Review of the subject diary indicates study drug compliance was 100% for the time period of November 30, 2010 – March 8, 2011.
- Subject 116 – The sponsor's data table indicates that this subject had treatment compliance less than 75% at Visit 11. Review of the clinic chart for Visit 11, which was performed on June 3, 2011, indicated that drug compliance was good. Review of the subject diary for the time period of March 4, 2011 – April 13, 2011 demonstrated good compliance. However the diaries for the time period of April 19, 2011 – July 21, 2011 were not completed properly by the subject.

*OSI Reviewer Comment: Dr. Luquez acknowledged the observations. Corrective action was indicated for all observations made. Dr. Luquez indicated that she will provide retraining to site personnel. The site also developed an SOP specific for electronic data entry, having data entry performed with a second person double checking electronic data entries.*

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

6. **Federico Perez Manghi, M.D.**

Viamonte 2278/80  
Buenos Aires  
C1056ABJ  
Argentina

- a. **What was inspected:** The inspection included review of the ethics committee approvals, the regulatory binder, delegation of duties, experience and training, CVs, financial disclosure, test article accountability and storage, adverse events, protocol deviations, and source records. For Study H9X-MC-GBDC, there were nine subject records reviewed. For Study H9X-MC-GBDD, there were 13 subject records reviewed. One-third of the informed consent documents of subjects screened and enrolled were reviewed.
- b. **General observations/commentary:** For Study H9X-MC-GBDC, there were 28 subjects screened and 26 subjects enrolled. For Study H9X-MC-GBDD, there were 45 subjects screened and 39 subjects enrolled. Per Argentina regulations, the study initially had to be reviewed and approved by both the national and local ethics review committees. In March 2011, the regulation changed and the national committee was not necessary. After that date only local approval was necessary. All approvals were in order. There were no 1572s submitted for the two studies.

There was adequate oversight of the two studies by the PI. There were no issues with the informed consents. Of the records reviewed, all inclusion/exclusion criteria were met. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable. There were some scattered protocol deviations and all were reported to the sponsor and the ethics committee.

In review of the test articles storage temperature logs, there were two days that the temperature was not recorded. By the date of this event, there was study drug stored at the site pharmacy refrigerator. There is a note in the log indicating that the thermometer was sent for calibration; the calibration company gave the site a temporary thermometer. However, the temperature for the two days was not recorded. *Review of the stability data from the application*

*looks good for 6 months at 30 degrees C.*

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**7. Jorge Waitman, M.D.**

Av. Velez Sarsfield 576 6 A  
Cordoba 5000  
Argentina\*

\*The study began at Dr. Waitman's site located below and moved to the above location in March 2012:

Fundacion Rusulleda & Blattle, Departamento  
De Nutricion, Metabolismo y Diabetologia  
Av. Colon 2057  
5003 Cordoba, Argentina.

- a. What was inspected:** The inspection included review of the ethics committee approvals and communications, experience and training, CVs, financial disclosure, and test article accountability. Five subject records were reviewed in depth to verify inclusion/exclusion criteria, concomitant medications, adverse events, and primary efficacy endpoints. For 17 subjects, sponsor data tables were verified for all HbA1c primary and secondary endpoints. The initial informed consent form (ICF) documents for all randomized subjects and one screen failure subject were reviewed. The re-consenting of subjects during the trial was reviewed for five subjects. The reason for subject withdrawals and SAE reporting were also audited against the sponsor data table for affected subjects.
- b. General observations/commentary:** There were 48 subjects screened at the site and 38 subjects enrolled. The first subjects were screened on July 12, 2010. Subject 251 was subsequently randomized on October 4, 2010. The last subject to have a study follow-up visit was identified as Subject 297 on October 17, 2012. The "OUS Investigator Listing Information" form was signed and dated by Dr. Waitman on April 8, 2008. There was no 1572 submitted.

Per Argentina regulations, the study initially had to be reviewed and approved by both the national and local ethics review committees. In March 2011, the regulation changed and the national committee was not necessary. After that

date only local approval was necessary. There were no issues with the informed consents and all ethics committee approvals were in order.

Source documentation was paper based. Data was later transferred to the electronic database by trained personnel. The site maintained documentation of subject communications and had various worksheets to record information during subject visits. Subject source documents were organized, maintained, legible and complete.

The clinical investigator followed the protocol approved by the EC in terms of subject selection, randomization scheme, required evaluations, administration of the test article, reporting of adverse events/serious adverse event, reporting on concomitant medications and frequency of follow-up. None of the subject records audited was found to be exceeding the maximum dosages per the Argentina labeling of the drugs. However, the inspection found a few instances when hypoglycemic reports were not recorded in the electronic database and one instance when a concomitant medication was not reported. For Subject 296, there were a few hypoglycemic events (6/20) found in the subject diary that were not entered into the electronic data base. For Subject 282, one use of antibiotics was not reported. These were considered isolated incidences and did not indicate a systemic problem with the data collected. Dr. Waitman verified that the inputting errors occurred and future corrective action was indicated.

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

## 8. Eli Lilly and Company

Lilly Corporate Center  
Indianapolis, Indiana 46285

- a. **What was inspected:** The inspection covered staff experience and training, sponsor oversight, contracts, operating procedures, site selection, and vendor selection. Monitoring files were reviewed during the inspection for 12 investigational sites (some of which had multiple protocols). Escalation summaries were reviewed for 2 sites.
- b. **General observations/commentary:** The sponsor showed adequate oversight of the clinical trials. Monitoring of the investigational sites was adequate. Appropriate steps were taken by the sponsor to bring noncompliant sites into

compliance, or if this could not be achieved, investigator sites were closed and the site closures were reported to the FDA with one exception. Dr. Rungby (Site #350 for Study H9X-MC-GBDD) was never brought into compliance prior to the last patient visit. The monitor indicated in her report that issues should have been escalated at the second interim monitoring visit (8/3/2011); however, this was only listed in the narrative and not the monitoring report's Issues section. At a subsequent monitoring visit, the monitor indicated that the site required more frequent monitoring visits and/or increased SDV; this did not occur. The issues at the site were not officially escalated until the monitoring visit on 11/16/2011. There was an escalation meeting on 4/26/2012, after the issue was increased to a Category 3 on 4/18/2012. The issue was considered closed as of 7/3/2012 because all patients had their last patient visit. According to the Director of Global Clinical Operations, the monitor was following the monitoring plan with regards to issue escalation, which did not require action to be taken as quickly as necessary. The new procedure (Version 2) does allow for quicker issue escalation and resolution. There were some instances in which SAEs were not monitored in a timely fashion, but the monitoring procedure was updated to remedy this also.

Although not systemic, 100% Source Data Verification (SDV) for specified subjects were not always performed in accordance with the Monitoring Plans, in that SDV would be performed on every 1st, 3rd, 5th and every 5th subject thereafter. There was no assurance, in some instances, that all areas indicated in the Monitoring Plan were being source data verified at each visit. Also, SDV was not always performed at each visit for the identified subjects, including the review of SAE's. In some instances, subject visits were not reviewed until several months later. For example, at Dr. Waitman's site, Subject 282 in Study H9X-MC GBDB experienced a Serious Adverse Event that was reported to the site on 4/4/2011. It was not monitored until 10/31/2011, although there were monitoring visits on 5/26-27/2011, 8/8-9/2011, and 10/6-7/2011.

At the time, the monitoring plan did not specify the time period when monitoring of serious adverse events was required. There was a revision to the procedure on 1/5/2012 (Version 2) which stated that monitoring of SAEs should "occur timely and be prioritized by CRA." The inspection revealed that review of SAEs was not later than the next monitoring visit after the revision.

The inspectional findings indicate adequate adherence to good clinical practice regulations. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this sponsor appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this BLA consisted of four domestic and three foreign clinical sites as well as the Sponsor.

Observations noted above for all clinical sites are based on the preliminary review of the Establishment Inspection Reports (EIRs). Observations noted above for the Sponsor are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

Three clinical sites inspected, Dr. Brusco, Luquez and Wynne, were each issued a Form FDA 483 citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). Dr. Wise was initially not issued a Form FDA 483, but had the classification upgraded to VAI after review of the EIR. Although regulatory violations were noted as described above for all four sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from these sites are acceptable for use in support of the indication for this application.

Drs. Manghi, Umpierrez, and Waitman and Sponsor Lilly were not issued a Form FDA 483; the classifications are all NAI (No Action Indicated). Data from these sites and the sponsor are considered reliable based on the available information.

In general, based on the inspection of the seven clinical sites (representing 12 protocol sites) and the Sponsor, the inspectional findings of these sites support validity of data as reported by the Sponsor under this BLA.

*{See appended electronic signature page}*

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/s/  
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CYNTHIA F KLEPPINGER  
06/06/2014

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06/06/2014

KASSA AYALEW  
06/06/2014



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
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Silver Spring, MD 20993

Date: May 14, 2014
From: CDR Alan Stevens, Reliability and Mechanical Engineering
OMPT/CDRH/ODE/DAGRID/GHDB
To: Dr. Abolade Adeolu, Regulatory Project Manager
OMPT/CDER/OND/ODEII/DMEP
Subject: CDRH Consult for BLA 125469, prefilled syringe and pen injector for subcutaneous of (b) (4) (dulaglutide [rDNA origin] injection)

Recommendation: Approve

Review Summary: My overall engineering assessment concludes that Eli Lilly has developed a reasonably safe and effective dulaglutide delivery system. Therefore, I recommend approval of the prefilled syringe and prefilled autoinjector for subcutaneous injection of dulaglutide. My review assessed the design and development of device constituent specifications for injection of dulaglutide, device engineering hazards analysis and risk controls, and performance and reliability studies, for each device constituent.

Not covered in my review are device human factors and device / drug compatibility.

I. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding BLA 125469. The device constituent of this combination product consists of a prefilled syringe and a pen injector.

II. Documents

Documentation for the device constituents were obtained from BLA 125469, eCTD location 3.2.P.7, 3.2.R.5 and 3.2.R.6. Also reviewed were the package labeling and medication guide.

III. Review

A. Indications for Use

Table with 2 columns: Product, Indications for Use. Row 1: (b) (4) (dulaglutide injection), (b) (4) TM is a glucagon-like peptide (GLP-1) receptor agonist... Row 2: (b) (4) Prefilled Syringe, The syringe is a disposable, prefilled delivery device...

(b) (4) Single-Use Pen	(b) (4) Single-Use Pen (Pen) is a disposable, prefilled delivery device. Each Pen contains one weekly dose of (b) (4) (0.75 mg / 0.5 mL or 1.5 mg / 0.5mL). Each Pen is for one-time use only.
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## B. Device Constituents

BLA 125469 contains two separate delivery devices: a prefilled syringe and a pen injector. Both devices contain one weekly dose of (b) (4) (0.75 mg / 0.5 mL or 1.5 mg / 0.5mL) and are single-use, disposable devices.

The prefilled syringe and pen injector comprise the finished delivery systems. Each of these systems shares the same container closure system, which is referred to in the BLA 125469 as the dulaglutide semi-finished syringe.

## C. Dulaglutide Semi-Finished Syringe

Information on the dulaglutide semi-finished syringe was obtained from BLA 125469, eCTD Section 3.2.P.7.

Shown in Figure 1 is the primary dulaglutide container closure. This part of the review is identifying the components and specifications. The referenced master files were not evaluated as part of the device review. The safety and effectiveness properties of the semi-finished syringe will be evaluated as part of the prefilled syringe and pen injector reviews.

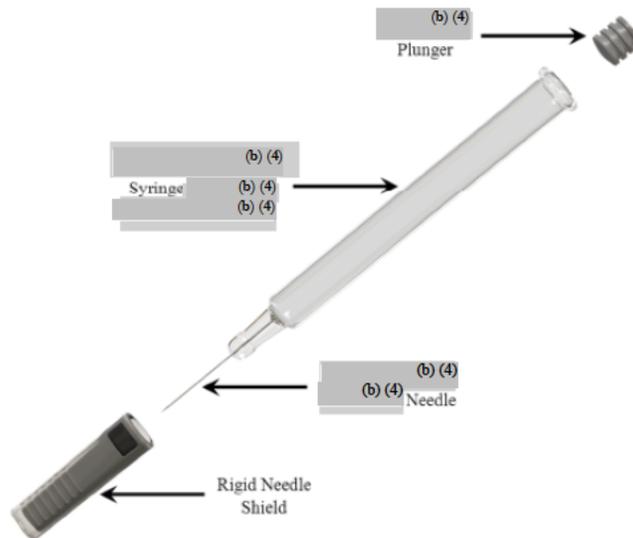


Figure 1

BLA 125469

Eli Lilly

Prefilled Syringe and Pen Injector for injection of (b) (4)

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Component/Process	Supplier	Drug Master File Number
Syringe (b) (4)	(b) (4)	
Needle Shield (b) (4)		
Plunger		
(b) (4)		



BLA 125469

Eli Lilly

Prefilled Syringe and Pen Injector for injection of (b) (4)

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**Semi-Finished Syringe – Break Loose Force and Glide Force Verification Studies**

The test report is found in Section 32P5, Control of Drug Product, “32p522-compression-proc”.

Testing is described to evaluate the break loose force and glide force for the semi-finished syringe and PFS configurations. These results are applicable to the PFS and SUP.

Methodology: A load cell is used to evaluate the forces required to initiate plunger movement and to maintain plunger movement.

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**D. (b) (4) Prefilled Syringe**

Information on the prefilled syringe was obtained from BLA 125469, eCTD Section 3.2.R.6. The finished prefilled syringe (Figure 5) includes the semi-finished syringe (Figure 1). Added to the semi-finished syringe are the label, (b) (4) and plunger rod. This is the same injection system used in the clinical trial, with the exception of the label and colors.

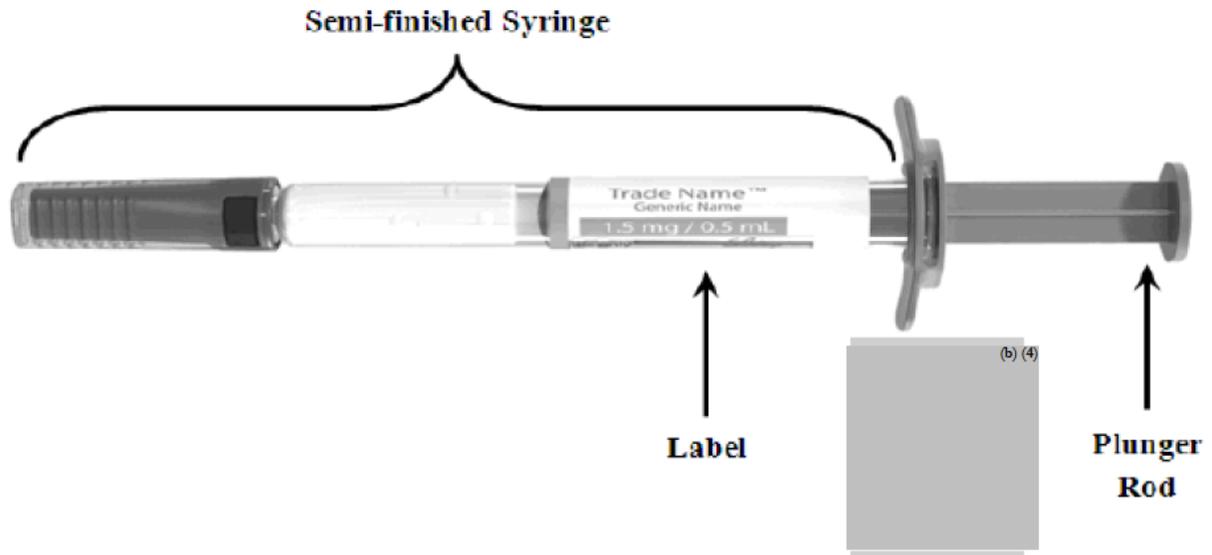


Figure 5

The prefilled syringe does not include fill level indicators or graduation marks because the product is a single dose, single use injection system. It is intended that the complete syringe volume will be injected and the empty syringe will be disposed.

The container closure (e.g., the semi-finished syringe) is filled in facilities claimed to be operating under Quality Systems in conformance to 21 CFR 210 and 21 CFR 211. Verification of this claim was not evaluated as part of the device review.

Two presentations are described: 0.75 mg / 0.5 mL and 1.5 mg / 0.5mL. Differentiation between the two presentations is by color and labeling.

Dose Strength	Color Code <sup>1</sup>
0.75 mg/0.5 mL	Yellow
1.5 mg/0.5 mL	Blue

<sup>1</sup> Plunger rod, (b) (4) and label are color coded according to the dose strength.

CDRH has developed device hazard checklists for syringes, which has been applied to this review. It is noted that many of the hazard causes are repetitive. The redundancies are included for completeness.

**Reviewer Comment: My overall assessment concludes that device engineering hazards analysis and risk controls are acceptable. Design verification studies are adequate and demonstrate reliable performance of the device constituent delivery system.**

**Table 1 – CDRH General Syringe Hazard Checklist**

Device Hazard	Cause	Applicable to (b) (4) PFS		Review Comments
		Yes	No	
				<i>This column will provide general comments on the applicable hazard. Many are related to manufacturing or drug compatibility with the container closure and are beyond the scope of the CDRH device review.</i>
Delivery Error/Delay in Therapy	Device Insufficiently Patent	X		This was evaluated as part of device non-clinical performance studies. Most likely causes of patency are manufacturing defects on the semi-finished syringe.
	Device Insufficiently Sealed to Environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Device Material Compromises Injectable	X		This is applicable, but would be caused by container closure contact with the drug, which is not covered within the CDRH device review.
	Device Volume Incorrect	X		See review of delivery accuracy testing.
	Insufficient Device Dimension	X		This would cause various failure modes that could result in delivery error (e.g. plunger rod dimension does not allow complete injection). Delivery accuracy studies demonstrate adequate design control.
	Insufficient or Compromised Visibility of Contents	X		The assembly causes do not apply to this review because the syringe is prefilled.

				Visibility hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Insufficient Device-User Interface	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers UI related hazards.
	Unexpected Separation of Components	X		Failure modes could occur during shipping, injection preparation, and injection. CDRH review of non-clinical performance studies notes adequate control of this issue.
	Inappropriate or Insufficient Connection		X	This hazard relates to syringes with luer type connections, which does not apply to the PFS.
	Drug Degraded	X		This is applicable, but would be caused by container closure contact with the drug, or drug stability, which are not covered within the CDRH device review.
	Insufficient Dose/Volume Markings/Graduations		X	The sponsor notes that no markings are on the PFS.
	Incorrect Device Assembly /Preparation	X		The assembly causes do not apply to this review because the syringe is prefilled. User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Incorrect Solution Uptake		X	Syringe is prefilled. This hazard relates to drawing up the medication from a vial.
	Incorrect Device Activation	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen).

				Although I have verified that the use related hazards analysis provided by the sponsor covers device activation related hazards.
	Incorrect Selection of Device	X		Device selection hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
Incorrect Therapy	Device Compromises Injectable	X		This is applicable, but would be caused by container closure contact with the drug, or drug stability, which are not covered within the CDRH device review.
	Improper Injection Site Selection	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers injection site selection related hazards.
Biological / Chemical Contamination	Device insufficiently sterile	X		Since the syringe is prefilled, the sterility issues should be addressed during drug manufacturing review / inspection. This is not being addressed by CDRH.
	Device Insufficiently Sealed to Environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Inappropriate or Insufficient Connection		X	This hazard relates to syringes with luer type connections, which does not apply to the PFS.
	Incorrect Device Assembly /Preparation	X		Since the syringe is prefilled, the contamination issues should be addressed during drug manufacturing review / inspection. This is not being addressed by CDRH.
	Inappropriate Device Re-use	X		Labeling indicates that the

				injection system is single use.
	Failure to Use Aseptic Technique	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers injection technique related hazards.
	Failure to Correctly Dispose Device	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers improper disposal related hazards.
Device allows for laceration	Device Breakage	X		The use related hazard analysis assesses the user ability to identify damaged syringe. The possibility of damage during injection was assessed during my review of non-clinical performance studies. No issues are noted.
	Device Exterior Surface Contains Sharp Edges	X		Review of injection system drawings do not identify any sharp edges, with the exception of the needle. The needle is a requirement of the injection system and mitigations have been implemented to reduce the risk associated with needle stick.
	Insufficient Assembly/Preparation	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers preparation related hazards.
	Inadequate Disposal	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards

				analysis provided by the sponsor covers improper disposal related hazards.
	Insufficient Activation	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers activation related hazards.
	Incorrect Assembly of device	X		The syringe is prefilled and presented to the user in its assembled form. Manufacturing related causes of incorrect assembly are deferred to inspection review.
Air Emboli	Device Insufficiently Sealed to Environment		X	Sponsor indicates that air emboli is not a risk to health for this combination product.
	Unexpected Separation of Components		X	
	Inappropriate or Insufficient Connection		X	
	Incorrect Device Assembly /Preparation	X		<p>The prefilled syringe IFU has a section on Commonly Asked Questions, one of which is "What if I see an air bubble in my syringe?". The response states "Air bubbles are normal. (b) (4) "</p> <p>The human factors study identifies <i>Attempts to Eliminate Air Bubble</i> as a use error observed during the study. The cause is identified as attempting to remove air from the syringe. It was observed that in some case <u>up to 1/3 of the syringe volume was lost due to this use error.</u></p> <p>The mitigation should be assessed as part of human factors and adequacy of labeling controls should be</p>

				considered.
Particulate Emboli	Device Insufficiently Patent	X		This will be evaluated as part of device non-clinical performance studies. Most likely causes of patency are manufacturing defects on the semi-finished
	Device Insufficiently Sealed to Environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Device Material Present within Injectable	X		This is applicable, but would be caused by container closure contact with the drug, or drug stability, which are not covered within the CDRH device review.
	Inappropriate or Insufficient Connection		X	This hazard relates to syringes with luer type connections, which does not apply to the PFS.
	Incorrect Device Assembly /Preparation	X		Since the syringe is prefilled, the contamination issues should be addressed during drug manufacturing review / inspection. This is not being addressed by CDRH.

**PFS Dose Accuracy**

The dose delivery specification for the (b) (4) PFS is 0.5mL (b) (4). Testing was conducted in accordance with ISO 11608-1:2012 - Needle-based injection systems for medical use — Requirements and test methods

BLA 125469

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Prefilled Syringe and Pen Injector for injection of (b) (4)

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Test Characteristic	Acceptance Criteria <sup>1</sup>	Design Specification Limits	Sample Size	Mean, $\bar{x}$	Standard Deviation $\pm\sigma$	Actual $K^{-1}$	Pass/Fail
<b>ISO 11608-1 Testing</b>							
Dose Accuracy at Standard Atmosphere, per ISO11608-1		(b) (4)	60			(b) (4)	Pass
Dose Accuracy at Cool Atmosphere, per ISO11608-1			60				Pass
Dose Accuracy at Warm Atmosphere, per ISO11608-1			60				Pass
Dose Accuracy after Dry Heat Preconditioning, per ISO11608-1			60				Pass
Dose Accuracy after Cold Storage Preconditioning, per ISO11608-1			60				Pass
Dose Accuracy after Free Fall Preconditioning, per ISO11608-1			21				Pass
Dose Accuracy after Vibration Preconditioning, per ISO11608-1			20				Pass

Preconditioning	Testing Condition	Dose Accuracy				Pass/ Fail
		Limits (mL)	Sample Size	Target K <sup>1</sup>	Actual K	
Standard: 23±5°C/ 50±25%RH for ≥ 4 hours	23±5°C/ 50±25% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Cool: 5±3°C for ≥ 4 hours	5±3°C		60			Pass
Warm: 40±2°C/ 50±10%RH for ≥ 4 hours	40±2°C/ 50±10% RH		60			Pass
Dry Heat: 30±2°C/ 65±5%RH for ≥ 96 hours	23±5°C/ 50±25% RH		60			Pass
Cold: 5±3°C for ≥ 96 hours	23±5°C/ 50±25% RH		60			Pass
Free Fall	23±5°C/ 50±25% RH		21			Pass
Vibration	23±5°C/ 50±25% RH		20			Pass

<sup>1</sup> The target k-value is, for a given sample size, the minimum actual k-value that will meet the pre-specified requirements for a quality attribute. Therefore, the actual k-value calculated for a sample must be greater than or equal to the target k-value to meet requirements.

**Design Verification**

Several design verification studies were conducted to verify specific functional requirements of the design, including forces required to initiate and maintain injection and force required to remove needle shield. Maintenance of these requirements following shipping simulation was also conducted.

Table Q4-5 (continued) PFS Design Verification Functional Results (Previously Submitted)

Test Characteristic	Acceptance Criteria <sup>1</sup>	Design Specification Limits	Sample Size	Mean, x	Standard Deviation ±σ	Actual K <sup>1</sup>	Pass/ Fail
<b>User Interaction Forces</b>							
Break Loose Force		(b) (4)	35			(b) (4)	Pass
Glide Force			35				Pass

<sup>1</sup> Refer to the Question 2 response for how target k is determined and how k<sub>act</sub> is calculated

**Table 3.2.R.6.3.2.2-1 Break Loose/Glide Force Testing Results**

Preconditioning	Testing Condition	Sample Size	Break Loose Force				Glide Force			
			Limit (N)	Target K	Actual K	Pass/Fail	Limit (N)	Target K	Actual K	Pass/Fail
Standard: 23±5°C/ 50±25%RH for ≥ 4 hours	23±5°C/ 50±25% RH	35	(b) (4)			Pass	(b) (4)			Pass

**Table 3.2.R.6.3.2.2-2 Needle Shield Removal Force Testing Results**

Preconditioning	Testing Condition	Sample Size	Needle Shield Removal Force			
			Limits (N)	Accept/Reject	# Outside Limits	Pass/Fail
Standard: 23±5°C/ 50±25%RH for ≥ 4 hours	23±5°C/ 50±25% RH	80	(b) (4)		0	Pass

**Table Q4-6 PFS Design Verification Functional Results (Not Previously Submitted)**

Test Characteristic	Acceptance Criteria	Design Specification Limits	Sample Size	Defects Observed	Pass/Fail
(b) (4)			80	0	Pass
(b) (4)			N/A <sup>1</sup>	N/A <sup>1</sup>	Pass
(b) (4)			N/A <sup>1</sup>	N/A <sup>1</sup>	Pass

<sup>1</sup> (b) (4) have been measured and verified to meet specification by the manufacturer (BD).

**Design Verification – Shipping Studies**

To demonstrate dose accuracy, container closure integrity, and acceptable user interaction forces of the prefilled syringe following exposure to transportation hazards, testing was performed on prefilled syringes subjected to simulated and field test shipments.

(b) (4)

(b) (4)

All dose accuracy measurements following the shipping studies met the requirement for 95% confidence that 95.0% of the doses delivered fell within the (b) (4) specification range.

**Table 3.2.R.6.3.3-1 Dose Accuracy Testing Results Following Shipping**

Shipment Type	Testing Condition	Sample Size	Dose Accuracy			
			Limits (mL)	Target K	Actual K	Pass/Fail
Simulation	23±5°C/ 50±25% RH	13	(b) (4)			Pass
Field Test			(b) (4)			Pass

**Table 3.2.R.6.3.3-2 Container Closure Integrity Test Results Following Shipping**

Shipment Type	Test Method	Quantity Tested	Results
Simulation	(b) (4)	20	Pass <sup>1</sup>
		20	Pass
Field Test		20	Pass <sup>1</sup>
		20	Pass

<sup>1</sup> Positive controls from testing of the batch showed (b) (4) acceptance criteria.

**Table 3.2.R.6.3.3-3 Break Loose/Glide Force Testing Results Following Shipping**

Shipment Type	Testing Condition	Sample Size	Break Loose Force				Glide Force			
			Limit (N)	Target K	Actual K	Pass/Fail	Limit (N)	Target K	Actual K	Pass/Fail
Simulation	23±5°C/ 50±25% RH	13	(b) (4)			Pass	(b) (4)			Pass
Field Test			(b) (4)			Pass	(b) (4)			Pass

**Table 3.2.R.6.3.3-4 Needle Shield Removal Force Testing Results Following Shipping**

Shipment Type	Testing Condition	Sample Size	Needle Shield Removal Force			
			Limits (N)	Accept/Reject	# Outside Limits	Pass/Fail
Simulation	23±5°C/ 50±25% RH	43	(b) (4)	0/1	0	Pass
Field Test			0		Pass	

**Shelf Life Results – The results are acceptable.**

Shelf life testing of the SUP is contained in Section 3.2.P.8.3.2 – supporting stability. Testing was conducted according to the following protocol (b) (4)

**Table 3.2.P.8.3.2.1.3-4 (continued) Supporting Stability Protocol for the Drug Product Packaged in Prefilled Syringes, Process Validation Batches**

Analytical Property	Method Type	Storage Conditions	Months											
			I <sup>1</sup>	0.5	1	2	3	6	12	18	T <sub>exp</sub>	24	30	
Functionality: Break Loose / Glide Force	Compression	2-8°C	-	-	-	X	X	X	X	X	X	X	X	X
		25°C/60% RH	I	-	X	-	X	X	-	-	-	-	-	-
		30°C/65% RH	-	X	X	X	-	-	-	-	-	-	-	-
Visual and Functional Inspection	Visual Inspection and Manual Operation	2-8°C	-	-	-	X	X	X	X	X	X	X	X	
		25°C/60% RH	I	-	X	X	X	X	-	-	-	-	-	
		30°C/65% RH	-	X	X	X	-	-	-	-	-	-	-	
Container Closure Integrity	Dye Ingress	2-8°C	-	-	-	-	-	-	X	-	-	X	X	

Abbreviation: I – Initial  
<sup>1</sup> The initial time point is considered to be (b) (4)  
 T<sub>exp</sub> = additional time point added at the batch expiration if a scheduled time point is not within 30 days of date of manufacture.

**Table 3.2.P.8.3.2.1.6.2-2 (continued) Stability Results for Validation Batch C038888B 1.5 mg/0.5mL, Prefilled Syringe**

Analytical Property	Acceptance Criteria <sup>1</sup>	Method	Condition	Time Point					
				Initial	2 Weeks	1 Month	2 Months	3 Months	6 Months
Other Tests									
Polysorbate 80 Concentration	(b) (4)	(b) (4)	2-8°C	(b) (4)					
			25°C/60% RH	(b) (4)					
			30°C/65% RH	(b) (4)					
Functionality: Break Loose Force	(b) (4)	Compression	2-8°C	(b) (4)					
25°C/60% RH			(b) (4)						
30°C/65% RH			(b) (4)						
Functionality: Glide Force	(b) (4)	Compression	2-8°C	(b) (4)					
25°C/60% RH			(b) (4)						
30°C/65% RH			(b) (4)						
Visual and Functional Inspection	(b) (4)	Visual Inspection and Manual Operation	2-8°C	(b) (4)					
25°C/60% RH			(b) (4)						
30°C/65% RH			(b) (4)						

N/A = Not Applicable  
<sup>1</sup> Acceptance criteria listed are those in effect at the start of the stability study.  
<sup>2</sup> Samples not tested due to shipping error to test laboratory.

**Biological Safety**  
 Biocompatibility and sterility of the drug and container closure are deferred to CDER review.

## E. (b) (4) Pen Injector

The single-use pen includes the dulaglutide semi-finished syringe. The single-use pen is intended to enable patients, caregivers or Health Care Professionals (HCP) to administer a single dose, subcutaneous injection of dulaglutide. The single-use pen Label provides information for drug product and dosage form as well as covering the mechanical apparatus within the single-use pen. The activation end incorporates a lock feature to prevent unintentional activation and an Injection Button to start the injection sequence. The injection end of the single-use pen incorporates a Base Cap for needle shield removal and Clear Base for stable positioning at injection site with 360 degree viewing of drug product.

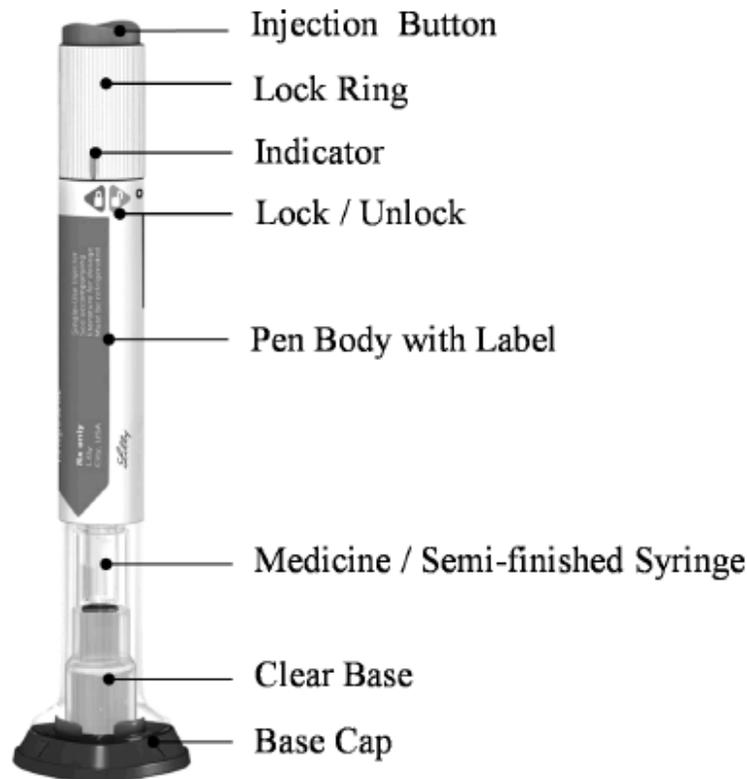


Figure 6

Dulaglutide injection is supplied as either 0.75 mg/0.5 ml or 1.5 mg/0.5 ml, and is a sterile, non-preserved solution for subcutaneous injection. The following single-use pens are available:

- Single-use pen, 0.75 mg - Each single-dose, prefilled single-use pen contains 0.75 mg of dulaglutide per 0.5 mL of solution.
- Single-use pen, 1.5 mg - Each single-dose, prefilled single-use pen contains 1.5 mg of dulaglutide per 0.5 mL of solution.

The single-use pen is prefilled with dulaglutide and is designed to deliver the entire dose in a single injection.

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The (b) (4) Pen Injector is available in dose strength presentations: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL. Each presentation is color coded according to the following table.

**Table 3.2.R.5.2.8.2-1 Dulaglutide Injection Single-use Pen Dose Strength Color Coding**

<b>Dose Strength</b>	<b>Color Code<sup>1</sup></b>
0.75 mg/0.5 mL	Yellow
1.5 mg/0.5 mL	Blue

<sup>1</sup> Single-use Pen label is color coded according to the dose strength.

**Table 2 - Pen Specifications**

<b>Characteristic</b>	<b>Designed Specification</b>
(b) (4)	

CDRH has developed device hazard checklists for pen injectors, which has been applied to this review. It is noted that many of the hazard causes are repetitive. The redundancies are included for completeness.

**Reviewer Comment: my overall assessment concludes that device engineering hazards analysis and risk controls are acceptable. Design verification studies are adequate and demonstrate reliable performance of the device constituent delivery system.**

**Table 3 – CDRH General Pen Injector Hazard Checklist**

Device Hazard	Cause	Applicable to (b) (4) Pen		Review Comments
		Yes	No	
Delivery Error/Delay in Therapy	Device fluid path occlusion	X		Sponsor provides fault tree analysis supported by evidence demonstrating that component failures are adequately addressed.
	Device alters/adds/retains contents	X		This is related to the leachable / extractables emanating from the semi-finished syringe. Review of these issues are deferred to CDER.
	Insufficient visibility of contents	X		Visibility hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Incomplete drug delivery	X		Sponsor provides fault tree analysis supported by evidence demonstrating that component failures are adequately addressed.
	Unexpected separation of components	X		Sponsor provides fault tree analysis supported by evidence demonstrating that component failures are adequately addressed.
	Excessive drug delivery			X

	Component failure	X		Sponsor provides fault tree analysis supported by evidence demonstrating that component failures are adequately addressed.
	Device insufficiently sealed to environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Device does not indicate amount of drug delivered/not delivered		X	This is not applicable to single-dose injectors.
	Insufficient dose/volume markings/graduation markings		X	This is not applicable to this single-dose injector.
	Incorrect device preparation	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Insufficient device activation	X		User activation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). Mechanical causes are covered in this review. Mechanical hazards preventing activation are adequately addressed by the sponsor.
	Injection initiates prior to needle reaching the correct tissue depth of penetration.	X		The sponsor has identified (b) (4) specification at which the injection will commence. This is covered in the review. Data demonstrates that this specification is reliably achieved. Sponsor also confirms that testing was conducted according to ISO 11608-5 methods, which is adequate demonstration that the hazard is controlled.
	Device used after expiration date	X		This is deferred to the CDRH human factors review. The labeling was verified to contain an expiration date.

				Also implicit in this hazard is that the combination product is safe and effective for use at or before the expiry. Review of shelf life information for the device verifies that the labeled storage conditions have been verified.
	Incorrect Selection of Device	X		Device selection hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Incorrect Injection Site	X		Injection site selection hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen).
Incorrect Therapy	Device Compromises Injectable	X		This is related to leachables causing adverse impact to the drug. Review of this issue is deferred to CDER.
	Improper Injection Site Selection	X		Injection site selection hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen).
Biological / Chemical Contamination	Device insufficiently sterile	X		This is important as it relates to the semi-finished prefilled syringe, which is being manufactured under drug manufacturing regulations. Therefore, review of this issue is deferred to CDER.
	Leachables released from device	X		Review of this issue is deferred to CDER.
	Inappropriate Storage	X		Shelf life issues related to the functionality of the pen injector have been adequately addressed by the sponsor.
	Device Insufficiently Sealed to Environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).

	Inappropriate or Insufficient Connection	X		Fault tree analysis demonstrates coverage and verification testing demonstrates the final design is adequate to believe that this hazard has been addressed.
	Incorrect Device Assembly /Preparation	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Inappropriate Device Re-use	X		The device is labeled as single-use. Device specifications are intended to permanently lock the device to prevent reuse.
	Failure to Use Aseptic Technique	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Failure to Correctly Dispose Device	X		Disposal related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). Protection from needle-stick and reuse are addressed by the device specifications to prevent exposure to these hazards.
Device allows for laceration	Device Body Breakage	X		These hazards are covered in this review.
	Needle Fracture / Remains Embedded in Subcutaneous Tissue	X		Sponsor has provided additional information (May 7, 2014) addressing needle fracture failure modes.
	Device Exterior Surface Contains Sharp Edges	X		Analysis of drawings does not identify any sharp edges.
	Insufficient Assembly/Preparation	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen

				that the study covered this hazard.
	Inadequate Disposal	X		Disposal related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). This review will cover any mechanical hazards relating to needle retraction features.
	Insufficient Activation	X		User activation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). Mechanical activation hazards are covered in this review.
	Incorrect Assembly of device	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
Air Emboli	Device Insufficiently Sealed to Environment		X	Sponsor indicates that air emboli is not a risk to health for this combination product.
	Unexpected Separation of Components		X	
	Inappropriate or Insufficient Connection		X	
	Incorrect Device Assembly /Preparation		X	
Particulate Emboli	Particulate released from device. Device Material Present within Injectable	X		The source would be the container closure. Review is deferred to CDER CMC reviewers.
	Incorrect Device Assembly /Preparation	X		As it relates to internal components properly interfacing / connecting to each other, this hazard will be covered in this review.

The following tables identify design verification studies and results for the SUP.

<p>(b) (4) <b>Pen Injector – Dose Accuracy</b></p> <p>The dose delivery specification for the (b) (4) Pen Injector is 0.5mL (b) (4). Testing was conducted in accordance with ISO 11608-1:2012 - Needle-based injection systems for medical use — Requirements and test methods.</p> <p><b>Reviewer Comments: Data provided by the sponsor demonstrates that the pen provides accurate</b></p>
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and repeatable delivery of the contents within the specified tolerances, (b) (4). Sponsor confirms that testing is conducted in accordance with ISO 11608-5 methods to assure delivery accuracy of automated injection devices.

Table 3.2.R.5.3.2.1.1-1 ISO 11608-1 Dose Accuracy Testing Results

Preconditioning	Testing Condition	Dose Accuracy				Pass/ Fail
		Limits	Sample Size	Target K <sup>1</sup>	Actual K	
Standard: 23±5°C/ 50±25%RH for ≥ 4 hours	23±5°C/ 50±25% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Cool: 5±3°C for ≥ 4 hours	5±3°C	(b) (4)	60	(b) (4)	(b) (4)	Pass
Warm: 40±2°C/ 50±10%RH for ≥ 4 hours	40±2°C/ 50±10% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Cold Storage: 5±3°C for ≥ 96 hours	23±5°C/ 50±25% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Free Fall	23±5°C/ 50±25% RH	(b) (4)	21	(b) (4)	(b) (4)	Pass
Vibration	23±5°C/ 50±25% RH	(b) (4)	20	(b) (4)	(b) (4)	Pass

<sup>1</sup> The target k-value is, for a given sample size, the minimum actual k-value that will meet the pre-specified requirements for a quality attribute. Therefore, the actual k-value calculated for a sample must be greater than or equal to the target k-value to meet requirements.

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**User Interaction Forces and Injection Time**

**Table 3.2.R.5.3.2.2-1 User Interaction Forces and Injection Time Test Results**

Test	Analytical Procedure	Acceptance Criteria	Sample Size	Target K	Actual K	Pass/Fail
		(b) (4)	60		(b) (4)	Pass
			60			Pass
			60			Pass
			60			Pass
			60			Pass

<sup>1</sup> Acceptance criteria for (b) (4) is based on an average. Actual mean force is (b) (4)

**Shipping Studies**

**Table 3.2.R.5.3.3-1 Leakage and Dose Accuracy Test Results following Pressure Change**

Test	Sample Size (n)	Acceptance Criteria/Limits	Average mL	Target K	Actual K	Pass/Fail
Visual Inspection for Leakage	25				(b) (4)	Pass
Dose Accuracy						Pass
						Pass

To demonstrate visual and functional performance of SUPs and secondary packaging following exposure to shipping hazards, visual and functional inspections were performed on packaged product subjected to a simulated shipment. The simulated shipping study included the following:

(b) (4)

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**Table 3.2.R.5.3.3-5 Dose Accuracy and Injection Process Time Test Results Following Shipping**

Shipment Type	Test / Limits	Sample Size	Test Results			Pass/Fail
Simulation	(b) (4)	35	Average (mL)	$p^*_{\text{required}}^1$	p-hat	
			(b) (4)			Pass
			(b) (4)			Pass
Field Test	(b) (4)	35	(b) (4)			Pass
			(b) (4)			Pass
			(b) (4)			Pass

<sup>1</sup> The  $p^*$  is, for a given sample size, the maximum estimated proportion of units outside of specifications that will meet the pre-specified requirements for a quality attribute. The estimated proportion of units outside of specifications is p-hat. Therefore, the p-hat for a sample must be less than or equal to the  $p^*$  to meet requirements.

**Shelf Life**

Shelf life testing of the SUP is contained in Section 3.2.P.8.3.2 – supporting stability.

Testing was conducted according to the following protocol ( (b) (4) ): (b) (4)

Table 3.2.P.8.3.2.1.3-1 (continued) Supporting Stability Protocol for the Drug Product (b) (4) Packaged in Single Use Pens,

Analytical Property	Method Type	Storage Conditions	Months							
			I <sup>1</sup>	0.25	0.5	1	3	6	9	12
Particulate Matter (b) (4)	(b) (4)	2-8°C	-	-	-	-	X	-	X	
		30°C/75% RH	I	X	X	X	-	-	-	
Color	(b) (4)	2-8°C	I	-	-	-	-	X	X	X
		30°C/75% RH	I	X	X	X	-	-	-	
Clarity	(b) (4)	2-8°C	I	-	-	-	-	X	X	X
		30°C/75% RH	I	X	X	X	-	-	-	
Polysorbate 80 Concentration	(b) (4)	2-8°C	I	-	-	-	-	X	-	X
		30°C/75% RH	I	X	X	X	-	-	-	
Dose Accuracy	(b) (4)	2-8°C	I	-	-	-	X	X	X	X
		30°C/75% RH	I	X	X	X	-	-	-	
Visual and Functional Inspection	(b) (4)	2-8°C	I	-	-	-	X	X	X	X
		30°C/75% RH	I	X	X	X	-	-	-	
Container Closure Integrity	(b) (4)	2-8°C	-	-	-	X	-	-	-	X

<sup>1</sup> The initial time point is considered to be (b) (4)

**Results: The results are adequate.**

Table 3.2.P.8.3.2.1.6.1-2 (continued) Stability Results for (b) (4) Validation Batch C156963C 0.75 mg/0.5mL, Single Use Pen

Analytical Property	Acceptance Criteria <sup>1</sup>	Method	Condition	Time Point (Weeks)		
				Initial	1	2
<b>Other Tests</b>						
Color	(b) (4)	(b) (4)	2-8°C 30°C/75% RH	(b) (4)		
Clarity	(b) (4)	(b) (4)	2-8°C 30°C/75% RH	(b) (4)		
Polysorbate 80 Concentration	(b) (4)	(b) (4)	2-8°C 30°C/75% RH	(b) (4)		
Dose Accuracy	(b) (4)	(b) (4)	2-8°C 30°C/75% RH	(b) (4)		
Visual and Functional Inspection	(b) (4)	(b) (4)	2-8°C 30°C/75% RH	(b) (4)		
Container Closure Integrity	(b) (4)	(b) (4)	2-8°C	(b) (4)		

N/A = Not Applicable

<sup>1</sup> Acceptance criteria listed are those in effect at the start of the stability study.

<sup>2</sup> Two initial time point samples were inadvertently analyzed for this test.

<sup>3</sup> Sample tested at 1 month of age.

**Labeled Storage Conditions**

The proposed storage condition for dulaglutide injection is refrigerated (2-8°C). The proposed storage time and condition for patient in use is 14 days at ambient temperature (not more than 30°C). Dulaglutide injection should be stored protected from excessive heat and from direct sunlight.

**Biological Safety**

Biocompatibility and sterility of the drug and container closure are deferred to CDER review.

Biocompatibility of the pen body materials are addressed in Section 3.2.R.5.3.1.

**Table 3.2.R.5.3.1-1 Patient Exposure Materials**

Patient Contacting Component	Material of Construction
Injection Button	(b) (4)
Lock Ring	(b) (4)
Base Cap	(b) (4)
Body Lower	(b) (4)
Baseplate	(b) (4)

The assessment provided by the sponsor concluded the safety of the identified components for use as a non-drug product contact materials of construction is demonstrated by a safe history of use in consumer products. These consumer product materials have substantial equivalence to the single-use pen in terms of frequency and extent of dermal contact under normal use conditions. Furthermore, published material testing, certifications, and material use in predicate devices provide additional justification the materials are safe for dermal contact. The evaluated materials of construction are consistent with the requirements of ISO 10993-1, pose no risk to patient or user safety, and no additional support of safety is required.

**IV. Previously Identified Deficiencies and Review of Additional Information**

Deficiencies

1. We have completed our review of the documentation submitted in support of the (b) (4) single use pen. During our review we evaluated the documentation to determine if hazards associated with the use of this device are adequately addressed. There are hazardous situations that do not appear to be explicitly addressed in your submission:

Hazardous Situation	
Delivery Error	Device fluid path occlusion
	Incomplete drug delivery
	Unexpected separation of components
	Component failure
	Device insufficiently sealed to environment

	Insufficient / inadequate device activation
	Injection initiates prior to needle reaching the correct tissue depth of penetration.
Contamination	Device Reuse
Trauma	Device Body Breakage
	Needle Fracture / Remains Embedded in Subcutaneous Tissue
	Unexpected separation of components

Please provide a system level hazard analysis (e.g. fault tree analysis) identifying the causes of these hazardous situations for the (b) (4) single use pen injector. For each identified cause, provide the following:

- a. Describe the control method for each identified cause.
- b. For each cause, provide an argument justifying the adequacy of the control to address the respective system hazard.
- c. Provide evidence verifying the control method adequately addresses the respective cause / hazard.

**Review:** The sponsor provided additional information demonstrating coverage of the hazards identified in my review. The additional information included description of risk management and design processes, fault tree analyses, and link to evidence demonstrating acceptability of design specifications and device safety requirements for injection of dulaglutide.

2. Many of the design verification studies present the results in the following format:

Test Characteristic	Acceptance Criteria	Sample Size	Target K	Actual K	Pass / Fail
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We are familiar with the use of tolerance limit factors when presenting design verification studies for pen injectors, and other delivery devices. However, the presentation of design verification results in your submission is not well understood. For example, we would generally expect to see results in the following format:

Test Characteristic	Acceptance Criteria	Sample Size	Mean, $\bar{x}$	Standard deviation, $\pm\sigma$	Lower / Upper Spec Limit, $x \pm k\sigma$	Pass / Fail
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Please provide the derivation of tolerance limit factor, k, to the Target K value and explain how this corresponds to the device performance. Alternatively, reformat the results into the expected format, as specified in the second table.

**Review:** Response provided by sponsor in April 4, 2014, amendment.  
 The information is adequate. My review of design verification studies has been updated accordingly.

3. There does not appear to be any performance evaluation on the needle to verify that the mechanical strength properties, patency, etc. are reliably achieved. Additionally, there does not appear to be information regarding manufacture of the needle and assurance that the manufacturing process reliably produces a needle that conforms to its specifications. Needle based hazards may be covered as part of the response to the hazardous situations, which is only related to the single use pen injector. However, please be sure to update the submission with specific information regarding the safe and effective use of the needle component of the prefilled syringe and single use pen injector.

**Sponsor Response**

The primary container for dulaglutide injection is a (b) (4) prefillable syringe (b) (4) with a (b) (4) needle and a rigid needle shield (RNS). The supplier of the prefillable syringe (b) (4) has certified the needle to meet the relevant performance requirements (b) (4)

Refer to Section 1.4.2 for the DMF Letters of Authorization (b) (4)

The (b) (4) is designed to ensure the needle performance is not impacted throughout semi-finished syringe and injector manufacturing, distribution, and handling. Two potential failure modes were identified for which the (b) (4) will not adequately protect the needle.

The first potential failure mode involves bending of the needle (b) (4) Failure Modes and Effects Analysis (FMEA) exercises have been conducted for each manufacturing operation and appropriate manufacturing controls have been implemented to reduce the occurrence rate of the failure and increase the probability of detection. In addition, Design Verification testing of the single-use pen included testing for needle bending during Basecap (and needle shield) removal (refer to the response to Question 4 for a summary of these test results).

The second potential failure mode involves the clogging of the needle (b) (4) FMEA exercises have been conducted (b) (4) and appropriate manufacturing controls have been implemented to reduce the occurrence rate of the failure and increase the probability of detection. In addition, the testing summarized below further demonstrates the capability of the needle component to meet the performance requirements of the prefilled syringe and single-use pen.

**Reviewer Comment: The additional explanation verifies the issues have been addressed. The response to this question is adequate.**

4. Section 3.2.P.5 includes specifications for the device constituents. Many of the device acceptance criteria are identified only as "Pass". This is not sufficient. Update the specifications with the specific acceptability criteria that will be applied, as verified and validated. Additionally, the list of specifications is not complete. For example, specifications for injection depth, activation

force, needle retraction time, injection force, locking mechanism override force, time between injection activation and injection initiation, etc. are not specified. Provide a complete list of device functional specifications with the corresponding acceptability criteria.

Response provided by sponsor in April 4, 2014, amendment.

The information is adequate. My review of design verification studies has been updated accordingly.

5. The break loose force and glide force testing (Section 3.2.P.5, Control of Drug Product, "32p522-compression-proc.pdf) for the semi-finished and prefilled syringe presentation appears to be a process capability test, rather than a design verification test. The acceptability criteria are not specified with respect to safety and effectiveness. Identify the design functional specifications on break loose force and glide force required for maintaining safe and effective drug delivery, and then provide the process capability testing demonstrating that the manufacturing process is producing the intended design.

**Sponsor Response**

*As noted in Section 3.2.P.2.4.1.4, Performance, the majority of variation in syringe delivery performance results from the (b) (4); therefore, studies were performed to ensure adequate delivery performance of the syringe (b) (4). These studies included the evaluation of break loose force, glide force, and injection time (b) (4). These data combined with historical delivery performance data were analyzed to determine the break loose force and glide force limits for the semi-finished syringe that were correlated to the prefilled syringe and single use pen being highly capable of meeting their respective design functional specifications. In addition, glide force limits were also determined for the prefillable syringe barrel, and manufacturing controls and specifications were implemented by the prefillable syringe barrel supplier to ensure robust control of delivery performance.*

**Reviewer Comment: The response is adequate with respect to verifying the performance of the product.**

6. The batch analysis results (Section 3.2.P.5.4) identifies tests, acceptance criteria, and results for the single use pen, prefilled syringe, and semi-finished syringe. Please address the following issues related to the device testing:
  - a. The visual inspection and functional inspection (manual operation) tests are not clearly described such that we understand what the tests entail. Further, the acceptance criteria are stated as "pass", which is not adequate. Update the table to include specifics of the visual and functional inspection tests and identify specific acceptance criteria.
  - b. Break loose force and glide force acceptance criteria are listed as an upper bound (e.g. NMT (b) (4) and NMT (b) (4) respectively) and no minimum force requirements are specified. (b) (4).  
Identify a lower limit on the force requirements for initiating and maintaining an injection and provide a justification for the acceptability criteria.

**Sponsor Response, #6a**

Overviews of the prefilled syringe (PFS) visual inspection and single-use pen (SUP) visual/function inspections are described in Sections 3.2.P.5.6.2.3 (PFS) and 3.2.P.5.6.3.4 (SUP). A statistical sample of finished combination products are manually inspected for attribute type defects by trained operators to ensure that predefined quality acceptance criteria have been met. The relevant quality acceptance criteria have been provided in the response to Question 4. The PFS and SUP visual and functional inspections are completed in addition to other variables tests (e.g., SUP dose accuracy and injection process time and PFS dose accuracy).

The PFS is inspected for glass and plastic component damage, needle shield fit, label appearance and other general cosmetic issues. Supporting stability studies were conducted to demonstrate that assembly of the semi-finished syringe into the prefilled syringe did not alter the stability profile of the dulaglutide drug product or have a negative impact on needle shield removal force, break loose force and glide force (see Section 3.2.P.8.1.5, Stability in the Prefilled Syringe). Therefore, a functional inspection is not completed during routine PFS batch release. Validation data for these properties was submitted in Table 3.2.P.5.4.2-1, Prefilled Syringe Validation Bath Analysis Data.

The SUP is visually inspected for similar defects as the PFS (e.g. glass and plastic component damage, Basecap fit, label appearance and other cosmetic issues). After the visual inspection, the functional inspection consists of (b) (4)

[REDACTED]. If any subsystem or operation does not function as intended, it is recorded as a defect.

All defects observed during either inspection are classified as Critical, Major or Minor based upon the potential impact to patient safety, relevant regulations, and/or the intended use of the product. Critical defects may result in a Serious Adverse Event (SAE) or regulatory noncompliance (for example: broken or cracked syringe, missing or incorrect label). Major defects may impact product quality attributes that could result in a non-serious adverse event (AE) or render the device inoperable for its intended use, (for example: cannot remove Basecap (SUP), missing (b) (4) (PFS)). Minor defects have negligible impact to therapeutic activity but may result in reduced performance and/or patient perception, (for example: non-biological foreign material on the device).

**Table Q6a-1 Prefilled Syringe Validation Batch Analysis Data**

Batch Number		<b>LYLE16A</b>	<b>C038888B</b>	<b>LYLF21A</b>
Semi-Finished Syringe Batch Number		LYLE16	C038888	LYLF21
Strength (mg/syringe)		0.75	1.5	1.5
Batch Size		(b) (4)		
Manufacturing Site		(b) (4)		
Date of Manufacture		12-DEC-2012	12-DEC-2012	11-DEC-2012
Batch Use		Validation	Validation	Validation
Visual Inspection <sup>1</sup>	N	500	500	500
	Critical ( (b) (4) )	0	0	0
	Major ( (b) (4) )	0	0	0
	Minor ( (b) (4) )	0	0	0
	Result	PASS	PASS	PASS

<sup>1</sup> Observed Defects: No defects observed

Table Q6a-2 SUP (b) (4) Process Validation Results

Batch Number		C038880H	C156963C	C156965A	C038888D
Semi-Finished Syringe Batch Number		C038880	LYLE16	LYLF21	C038888
Strength (mg/syringe)		0.75	0.75	1.5	1.5
Batch Size		(b) (4)			
Manufacturing Site		Eli Lilly	Eli Lilly	Eli Lilly	Eli Lilly
Date of Manufacture		19-Jun-2013	21-Jun-2013	25-Jun-2013	24-Jun-2013
Batch Use		Validation	Validation	Validation	Validation
Visual/Functional Inspection <sup>1</sup>	N	500	500	500	500
	Critical (b) (4)	0	0	0	0
	Major (b) (4)	1	2	0	0
	Minor (b) (4)	1	0	0	0
	Result	PASS	PASS	PASS	PASS

<sup>1</sup> Observed Defects:

- C038880H – (b) (4)
- C156963C – (b) (4)
- C156965A – No defects observed
- C038888D – No defects observed

Table Q6a-3 SUP (b) (4) Process Validation Results

Batch Number		C038880F	C109851A	C109847A	C038888A
Semi-Finished Syringe Batch Number		C038880	LYLE16	LYLF21	C038888
Strength (mg/syringe)		0.75	0.75	1.5	1.5
Batch Size		(b) (4)			
Manufacturing Site		Eli Lilly	Eli Lilly	Eli Lilly	Eli Lilly
Date of Manufacture		20-DEC-2012	14-DEC-2012	03-DEC-2012	01-DEC-2012
Batch Use		Validation	Validation	Validation	Validation
Visual/Functional Inspection <sup>1</sup>	N	500	500	500	500
	Critical (b) (4)	0	0	0	0
	Major (b) (4)	0	0	0	1
	Minor (b) (4)	1	0	1	1
	Result	PASS	PASS	PASS	PASS

<sup>1</sup> Observed Defects:

- C038880F – (b) (4)
- C109851A – No defects observed
- C109847A – (b) (4)
- C038888A – (b) (4)

Sponsor Response, #6b

(b) (4)

**Reviewer Comments: The sponsor has provided acceptable justification to support the current device constituent specifications.**

7. The shipping simulation testing results for the single use pen indicates on major defect following testing (Table 3.2.R.5.3.3-6). Please describe the observed defect, describe the impact to the patient from the defect and provide a risk assessment.

Sponsor Response

(b) (4)



(b) (4)

**Reviewer Comment – The additional explanation is adequate.**

8. The (b) (4) single use pen instructions for use references the Medication Guide for complete information about proper storage; however, the Medication Guide does not appear to include any storage information. Please correct the discrepancy.

The requested information was added to the Medication Guide (See May 6, 2014 amendment, Sequence 0017)

## V. Decision Recommendation

I recommend approval of the prefilled syringe and prefilled autoinjector for subcutaneous injection of dulaglutide. My overall assessment concludes that device engineering hazards analysis and risk controls are acceptable. Design verification studies are adequate and demonstrate reliable performance of the device constituent delivery system.

Digital Signature Concurrence Table	
Reviewer	
Supervisor	

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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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ABOLADE ADEOLU

05/15/2014

Administratively checked into DARRTS by Project Manager on behalf of the reviewer

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**HUMAN FACTORS, LABEL, AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** March 13, 2014

**Requesting Office or Division:** Division of Metabolic and Endocrinology Products (DMEP)

**Application Type and Number:** BLA 125469

**Product Name and Strength:** Trulicity  
(dulaglutide)  
Injection  
1.5 mg/0.5 mL

**Product Type:** Combination (drug + device)

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Eli Lilly and Co.

**Submission Date:** September 17, 2013

**OSE RCM #:** 2013-2185

**DMEPA Primary Reviewer:** Sarah K. Vee, PharmD

**DMEPA Team Leader:** Yelena Maslov, PharmD

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### 1. REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested DMEPA evaluate the Applicant's Human Factor Validation Study Results as well as the container label, carton labeling, and Instructions for Use (IFU) associated with the proposed new product Trulicity (dulaglutide), to ensure the intended population is able to use the product safely and effectively.

### 2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS) (N/A)	B
ISMP Newsletters (N/A)	C
Previous DMEPA Reviews (N/A)	D
Human Factors Study (prefilled syringe)	E
Human Factors Study (single use pen)	F
Container Label, Carton Labeling, and Instructions for Use (IFU) or Medication Guide	G

N/A=not applicable for this review

### 3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

#### 3.1 Prefilled Syringe

Overall, human factors study results demonstrated that dulaglutide prefilled syringe can be used safely and effectively by trained users. Although some errors have occurred with untrained users, it appears that the errors did not appear unique (i.e., pushing the plunger all the way, inserting the needle at 45 degree angle, etc.). We also note that we do not ordinarily require human factors study for prefilled syringes because this product design configuration has been used widely among patients with diabetes for many years. Thus, the results from the human factors study represent information that is already known about the use of prefilled syringes. As a result, we find the results of the human factors study acceptable.

#### 3.2 Single Use Pen

Overall, human factors study results demonstrated that trained participants are able to use the dulaglutide single use pen (SUP) safely and effectively. However, some untrained users encountered difficulties while administering this product using the SUP. We note that the

difficulties this user group encountered have also been reported with the use of injection pen devices and therefore we do not believe that the risks are unique to the proposed pen (i.e. press and hold the green injection button, hold the clear base of the SUP firmly against the skin until a second click is heard). Failure to perform these tasks would result in underdoses in most instances.

We note that three failures occurred with the SUP that would have resulted in needle stick injury and missed doses (i.e. 3 untrained participants held the SUP upside down). The design of the SUP is such that the needle is hidden from view leading to a possible misunderstanding of the orientation of the SUP and potential medication errors. Although holding the SUP upside down would possibly result in injection of the drug into the thumb, the resulting adverse event would be needle stick injury. Unlike epinephrine, however, although undesired, injection of dulaglutide into the thumb would not result in a medical emergency (i.e. potential loss of the digit).<sup>1,2</sup> This type of error is also not unique to the SUP; thus, we find the results of the human factors study acceptable. But we recommend that training be provided before first use of the product to ensure safe and effective use of the devices to deliver the dose of dulaglutide due to the errors that have occurred with this pen.

We further provide comments in Section 4.1. Recommendations for the Applicant, to also improve the IFU to help mitigate these task failures.

#### **4. CONCLUSION & RECOMMENDATIONS**

The Human Factors Study demonstrated that trained users are able to use the pen and prefilled syringe safely and effectively. However, some untrained users may encounter difficulties while administering this product. As a result, DMEPA concludes that proper education and training prior to first injection of dulaglutide is desirable to promote the correct use of the product.

The proposed IFU, container label, carton and insert labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product, to mitigate any confusion, and to clarify information.

##### **4.1 RECOMMENDATIONS FOR THE APPLICANT**

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

###### **4.1.1 Prefilled Syringe Instructions for Use**

A. Revise the numbered instructions as indicated below. We recommend this because several patients missed the bulleted lists under these steps as they may not read the bullet points.

1. Pull off and throw away the needle cover

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<sup>1</sup> Hardy SJ, Agostini DE. Accidental epinephrine auto-injector induced digital ischemia reversed by phentolamine digital block. *J Am Osteopath Assoc* 1995;95(6):377–8.

<sup>2</sup> Kaspersen J, Vedsted P. Accidental injection of adrenaline in a finger with EpiPen. *Ugeskr Laeger* 1998;160(45):6531–2. [[PubMed](#)]

2. Gently pinch a skin fold at the injection site
  3. Insert the needle at 45 degree angle into your skin
  4. Slowly push the plunger all the way in until all the medicine is injected
  5. Remove the needle from your skin
  6. Gently let go of the fold of your skin
  7. Throw away the syringe in a puncture resistant container
- B. Revise the pictures associated with the steps to ensure they match the descriptions of each step.

#### **4.1.2 Single Use Pen Instructions for Use**

- A. Revise the numbered instructions as indicated below. We recommend this because of several patients missed the bulleted lists under these steps as they may not read the bullet points.
1. Pull off and throw away the (b) (4) base cap
  2. Place the clear base flat and firmly against your skin at the injection site
  3. Unlock by turning the Lock Ring
  4. Press and hold the green injection button until you hear a loud click
  5. Hold in place (b) (4) until you hear a second click and (b) (4)
  6. Remove the pen from your skin
  7. Throw away the pen in a puncture resistant container
- B. Revise the pictures associated with the steps to ensure they match the descriptions of each step.

#### **4.1.3 Prefilled Syringe Container Label and Carton Labeling**

- A. Add the statement “Single Use Only”
- B. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.
- C. Ensure that the image of the prefilled syringe accurately represents the actual size, shape, color, and imprint of the commercial product and is not a schematic or computer-generated image. In addition, this image should be less prominent than the proprietary name, established name and strength.<sup>3</sup>

#### **4.1.4 Single Use Pen Container Label and Carton Labeling**

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<sup>3</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

A. See 4.1.3 B and 4.1.3 C

If you have questions or need clarifications, please contact Lyle Canida, project manager, at 301-796-1637.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Dulaglutide that Eli Lilly submitted on September 17, 2013.

<b>Table 2. Relevant Product Information for Dulaglutide</b>	
<b>Active Ingredient</b>	dulaglutide
<b>Indication</b>	glucagon-like peptide (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
<b>Route of Administration</b>	subcutaneous injection
<b>Dosage Form</b>	Solution
<b>Strength</b>	1.5 mg/0.5 mL
<b>Dose and Frequency</b>	1.5 mg once weekly
<b>How Supplied</b>	Single use pen or prefilled syringe
<b>Storage</b>	Refrigerate at 36°F to 46°F (2°C to 8°C), up to the expiration date
<b>Container Closure</b>	The primary container closure system for dulaglutide injection is a (b) (4) syringe (b) (4) closed with an (b) (4) plunger and rigid needle shield. Syringe (b) (4)

## APPENDIX E. HUMAN FACTORS STUDY: Prefilled Syringe (PFS)

### E.1 Study Design

#### Study Participants

Approximately half of the participants (n=48) were provided a training session focusing on the key steps for preparing for the injection, administering the injection, and disposing of the PFS. The training condition was assigned randomly and balanced across participants while ensuring a minimum of 15 trained and 15 untrained per distinct user group. This training was intended to be representative of the type of training that a patient may receive from their health care provider.

One-on-one training comprised a step-by-step demonstration of the entire injection process while pointing to each step in the IFU. The participant practiced the entire process one time, using the IFU, with the moderator assisting as necessary to ensure a successful injection into an injection pad.

The training session averaged about 15 minutes in length for most participants. The moderator then escorted the participant to a waiting area for a training decay period lasting no less than one hour.

Experience Group	Injection Naïve Patients	Injection Experienced Patients	Caregivers	Subtotals
No Impairment	12	18	31	61
Vision Impairments	3	6	--	9
Hand Impairments	7	2	--	9
Hand and Vision Impairments	8	6	--	14
Subtotals	30	32	31	
Total	93			

#### Study Protocol

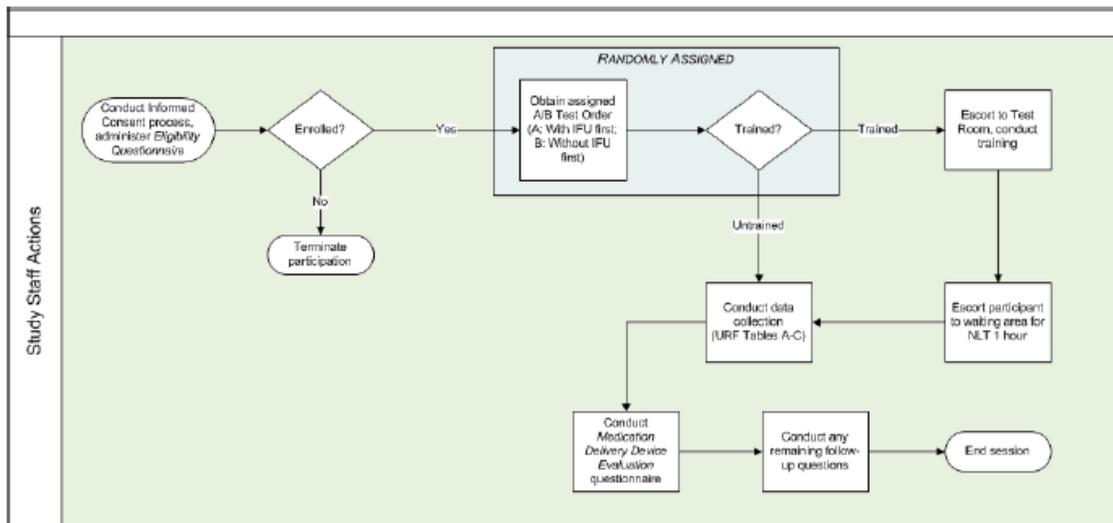
Following either the informed consent process (for untrained participants) or the training decay period (for trained participants), the participant was escorted to the study room. The moderator provided a new carton of devices to each participant, giving them the opportunity to briefly and independently familiarize themselves with the test materials. Participants were further instructed to behave as they would at home, with no specific instructions or time limit given.

All participants performed two injections into a surrogate injection pad. One injection was performed with access to the IFU and QRG, and one injection was administered without any access to the IFU and QRG. The order of the test cases was randomly assigned and balanced across participants.

For each attempt, participants had access to the PFS carton, IFU and QRG (if required), injection pad, trash can, and a sharps container.

Before each attempt, the moderators asked the participant to point to where they intended to simulate performing the injection; strapping the pad to the location if the selected site was appropriate.

Following the usability test, the moderator gave the participant the IFU and asked a series of knowledge-based questions that required them to use the IFU and QRG to answer. Correct and incorrect answers were documented in the URF. Afterwards, the moderator conducted a followup interview, probing as necessary to understand and document any sources of participant confusion in the IFU.



**Critical/Priority Tasks:**

- Remove from storage and open the package in home use
- Inspection of the PFS to ensure that it is not expired or damaged
- Slowly push the Plunger all the way in until all the medication is injected

## E.2 Results for Critical/Priority Tasks

### 1. Inspect the PFS to be sure it is not damaged or expired

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
2	Inspect the PFS to be sure it is not damaged or expired	√	104 (55.9%)	Fails to check expiration date	6	70	76
				Fails to inspect syringe for damage	6	39	45

### 2. Slowly push the Plunger all the way in until all the medication is injected

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
8	Slowly push the Plunger all the way in until all the placebo is injected (injection pad will be used in this study)	√	169 (90.9%)	Starts injection before inserting needle	1	12	13
				Partially pushes the plunger	1	2	3
				Moves angle of syringe while pushing the plunger	1	0	1

### Table of Errors for All Tasks

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
1	Remove the PFS and the IFU from the package		186 (100.0%)	Fails to/Unable to open package	0	0	0
				Fails to/Unable to remove device from package	0	0	0
				Exposes device to shock or vibration (drops, rough handling)	0	0	0
				Remove from Package – Other	0	0	0

2	Inspect the PFS to be sure it is not damaged or expired	√	104 (55.9%)	Fails to check expiration date	6	70	76
				Fails to inspect syringe for damage	6	39	45
				Inspect – Other	0	0	0
3	Wash your hands (can be simulated in this study)		99 (53.2%)	Does not wash hands	25	62	87
4	Select the injection site (injection pad will be used in this study)		177 (95.2%)	Selects improper site	2	7	9
5	Pull off and discard the needle cover		154 (82.8%)	Fails to/Unable to remove needle cover	0	0	0
				Holds syringe by plunger rod	1	0	1
				Pulls or pushes on plunger rod	1	2	3
				Fails to discard needle cover	1	29	30
				Touches needle	0	0	0
				Remove Needle Cover - Other	0	0	0
6	Gently grasp a fold of skin at the injection site (injection pad will be used in this study)		160 (86.0%)	Fails to pinch injection site	5	19	24
				Pinches inadequate amount	0	2	2
7	Insert the needle into the skin at about a 45		146 (78.5%)	Needle inserted at any angle other than ~45 degrees	3	37	40
				Does not insert needle	0	0	0

	degree angle (injection pad will be used in this study)			Exposes device to shock or vibration (drops, rough handling)	0	0	0
				Touches needle	0	0	0
8	Slowly push the Plunger all the way in until all the placebo is injected (injection pad will be used in this study)	√	169 (90.9%)	Starts injection before inserting needle	1	12	13
				Fails to / Unable to push the plunger	0	0	0
				Partially pushes the plunger	1	2	3
				Moves angle of syringe while pushing the plunger	1	0	1
				Give Injection – Other	0	0	0
9	Remove the needle from the skin (injection pad will be used in this study)		186 (100.0%)	Removes syringe while injecting	0	0	0
				Removes needle at different angle than inserted	0	0	0
10	Gently let go of the fold of skin (injection pad will be used in this study)		182 (97.8%)	Releases pinch before injection is complete	0	4	4
11	Dispose of the PFS in a puncture-resistant sharps container		138 (74.2%)	Improper disposal	0	31	31
				Attempts to reattach needle cover	3	35	38
				Dispose- Other	0	0	0
				Exposes device to shock or vibration (drops, rough handling)	0	0	0
					56	351	407

## APPENDIX F. HUMAN FACTORS STUDY: Single Use Pen (SUP)

### F.1 Study Design

#### Study Participants

Participants included three user groups including both men and women of various ages, visual impairments (e.g. glasses or retinopathy), range of dexterity, and educational background. The user groups were made up of Type 2 diabetic patients as per the proposed indications for the product. The study also included healthcare practitioners (including registered nurses, endocrinologists, pharmacists, diabetes educators, licensed practical nurses, and medical assistants).

Experience Group	Injection Naïve Patients	Injection Experienced Patients	Caregivers	HCP	Subtotals
No Impairment	17	22	29	30	98
Vision Impairments	6	5	1	--	12
Hand Impairments	5	8	--	--	13
Hand and Vision Impairments	2	3	--	--	5
Subtotals	30	38	30	30	
Total	128				

Training was provided to 64 participants for all groups. The moderator used the IFU to walk the participant through the correct use of the device, and allow the participant to perform a practice injection. A training decay of at least one hour was built into the study to simulate the potential lapse in time between patients receiving training and their attempt to use the device.

#### Study Protocol

Following either the informed consent process (for untrained participants), or the training decay period (for trained participants), the participant was escorted to the study room.

The moderator provided a new carton of devices to each participant, giving them the opportunity to briefly and independently familiarize themselves with the test materials. Participants were further instructed to behave as they would at home, with no specific instructions or time limit given. Caregivers were allowed to interact with their patient partner during this orientation time as they may have at home. HCPs were instructed to behave as they normally would to prepare for administering an injection to a patient, and to let the moderator know when they were ready for their patient partner to be brought into the room. Following this self-guided orientation, the study materials were repackaged to be used by the participants for data collection.

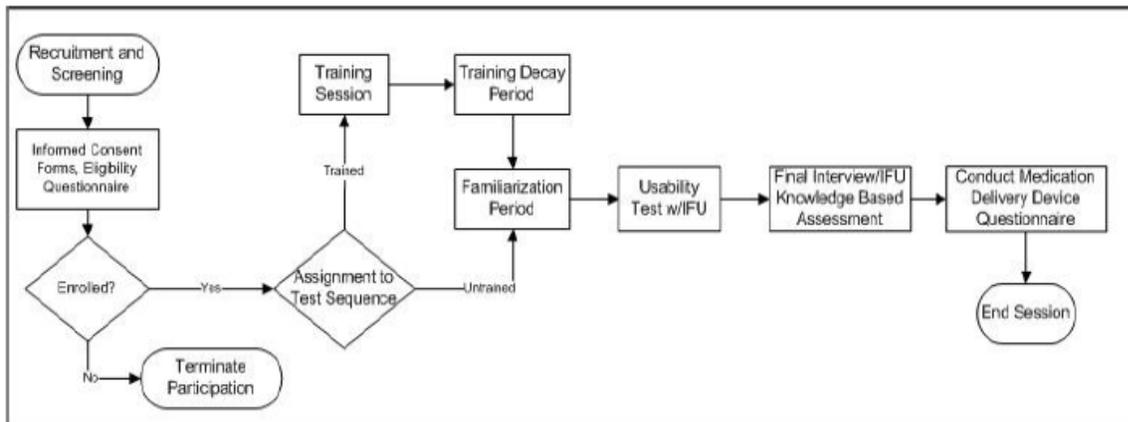
All participants performed one injection of placebo. For the injection, participants had access to the SUP carton, IFU and QRG, hand sanitizer, alcohol wipes, cotton balls, latex/nitrile gloves, trash can, and a sharps container.

At the beginning of data collection and before the injection, the moderators asked the participant to point to where he/she intended to perform the injection; allowing the participant to proceed if the selected site was appropriate (i.e., abdomen or thigh for patients; patient's abdomen, thigh, or arm for caregivers and HCPs). HCPs were asked this before their patient partner was brought into the room.

If a participant selected an incorrect site, the error was recorded and noted for discussion later, and a proper injection site was selected by the moderator without explanation.

After the injection, the moderator conducted a post-use interview to confirm the use errors noted on the URF and probe as necessary to understand and document the cause of any and all use errors, close calls and operational difficulties. The investigation included discussion of the extent to which observed failures may be due to aspects of the design of the device, labeling, training, IFU, carton or QRG.

Following the post-test interview, the moderator gave the participant the IFU and asked a series of knowledge-based questions that required him/her to use the IFU and QRG to answer. Correct and incorrect answers were documented in the URF. Afterwards, the moderator conducted a follow-up interview, probing as necessary to understand and document any sources of participant confusion in the IFU.



### Critical/Priority Tasks

- Remove from storage and open the package in home use
- Pull off and discard the base cap
- Inspect the SUP to be sure it is not damaged or expired
- Place the clear base of the SUP flat and firmly against the skin at the injection site
- Press and hold the green injection button

- Remove the SUP from skin after injection
- Dispose of the SUP in a puncture-resistant sharps container

## F.2 Results

1. Remove the SUP and the IFU from the package (No errors)
2. Inspect the SUP to be sure it is not damaged or expired. Most people mentioned that others check (e.g. pharmacist, spouse) or assumed it was safe to use since it was handed to them.

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
2	Inspect the SUP to be sure it is not damaged or expired	Priority	74/128 (57.8%)	Fails to check expiration date	3	43	46
				Fails to inspect pen for damage	1	30	31
				Fails to check drug (clear, not cloudy)	5	28	33

3. Pull off and discard the gray base cap

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
3	Pull off and discard the gray base cap	Critical	109/128 (85.2%)	Fails to / Unable to remove base cap	1	1	2
				Fails to discard base cap	0	17	17
				Unlocks SUP and presses button before removing base cap	1	1	2

- a. Fails to/unable to remove base cap & Unlocks SUP and presses button before removing base cap. The trained participant “forgot” to remove the base cap. The untrained participant thought the needle would push through the cap, did not consult the IFU. Both realized that they injected into the cap.
- b. Replaces Cap Before injection: 1 untrained participant removed based cap, replaced the base cap to review a step in the IFU. 1 untrained caregiver removed the base cap, decided to clean the injection site, and recapped the SUP to do so.

4. Place the clear base of the SUP flat and firmly against the skin at the injection site

Step	Use Step (Task)	Critical/Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
4	Place the clear base of the SUP flat and firmly against the skin at the injection site	Priority	117/128 (91.4%)	Selects improper site	1	6	7
				Unlocks and presses button before placing on skin	0	1	1
				Places SUP upside down/inverts	0	3	3

- a. Selects Improper Site: 3 untrained participants (injection-naïve) were confused over the IFU while others chose the site that they normally receive other injections/shots.
- b. Unlocks and presses button before placing on skin: The participant inadvertently pressed the button.
- c. Places SUP upside down/inverts: 1 HCP assumed it worked like an EpiPen. 1 caregiver thought the locking mechanism would be close to the needle. 1 participant thought that it was a like a syringe, with the broader part for thumb.

5. Unlock by turning the lock ring (No errors)

6. Press and hold the green injection button

Step	Use Step (Task)	Critical/Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
6	Press and hold the green injection button	Priority	107/124 (86.3%)	Pinches up skin	6	10	16
				Incomplete button press (does not start injection or does not stay down)	0	2	2

- a. Incomplete Button Press (does not start injection or does not stay down): Both did not press the button hard enough to actuate the SUP.
- b. Pinches up skin: They all did what they would normally to for an injection.

7. Hold the clear base of the SUP firmly against the skin until a second click is heard (this occurs within 5-10 seconds) (Trained = 2; Untrained = 6).

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
7	Hold the clear base of the SUP firmly against the skin until a second click is heard (this occurs within 5-10 seconds)		113/121 (93.4%)	Removes SUP before device retracts	2	6	8

4 untrained participants thought injection would be complete immediately after pressing the button. 1 untrained participant counted 5 seconds too fast. 1 untrained participant relied on watching the plunger descend. 2 trained participants thought they had lifted after the second click.

8. Remove the SUP from skin after injection (No errors)  
 9. Dispose of SUP in a puncture- resistant sharps container

Step	Use Step (Task)	Critical/ Priority Task	Total Completion Rate (n=186)	Potential Use Errors	Use Error Count		
					Trained	Untrained	Total
9	Dispose of SUP in a puncture-resistant sharps container	Priority	85/123 (69.1%)	Improper Disposal	1	27	28
				Attempts to re-lock device	1	4	5
				Replaces base cap	0	21	21

- a. Improper Disposal  
 b. Attempts to relock device: 4 stated it was safer to relock and 1 thought relocking would retract the needle.  
 c. Replaces Cap After injection: 17 said they recapped for safety reasons. 2 thought the SUP was reusable.

## **APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE**

### **G.1 List of Label and Labeling Reviewed**

We reviewed the following dulaglutide labels and labeling submitted by Lilly on September 17, 2013.

- Container label
- Carton labeling
- Instructions for Use
- Medication Guide

### **G.2 Label and Labeling Images**

(b) (4)



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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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SARAH K VEE  
03/13/2014

YELENA L MASLOV  
03/19/2014



Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** March 12, 2014

**From:** CDR Alan Stevens, Reliability and Mechanical Engineering  
OMPT/CDRH/ODE/DAGRID/GHDB

**To:** Dr. Abolade Adeolu, Regulatory Project Manager  
OMPT/CDER/OND/ODEII/DMEP

**Subject:** CDRH Consult for BLA 125469, prefilled syringe and pen injector for subcutaneous of (b) (4) (dulaglutide [rDNA origin] injection)

## I. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding BLA 125469. The device constituent of this combination product consists of a prefilled syringe and a pen injector.

## II. Documents

Documentation for the device constituents were obtained from BLA 125469, eCTD location 3.2.P.7, 3.2.R.5 and 3.2.R.6. Also reviewed were the package labeling and medication guide.

## III. Review

### A. Indications for Use

Product	Indications for Use
(b) (4) (dulaglutide injection)	(b) (4)™ is a glucagon-like peptide (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
(b) (4) Prefilled Syringe	The syringe is a disposable, prefilled delivery device. Each Syringe contains one weekly dose of (b) (4) (0.75 mg / 0.5 mL or 1.5 mg / 0.5mL). Each Syringe is for one-time use only.
(b) (4) Single-Use Pen	(b) (4) Single-Use Pen (Pen) is a disposable, prefilled delivery device. Each Pen contains one weekly dose of (b) (4) (0.75 mg / 0.5 mL or 1.5 mg / 0.5mL). Each Pen is for one-time use only.

### B. Device Constituents

BLA 125469 contains two separate delivery devices: a prefilled syringe and a pen injector. Both devices contain one weekly dose of (b) (4) (0.75 mg / 0.5 mL or 1.5 mg / 0.5mL) and are single-use, disposable devices.

The prefilled syringe and pen injector comprise the finished delivery systems. Each of these systems shares the same container closure system, which is referred to in the BLA 125469 as the dulaglutide semi-finished syringe.

### C. Dulaglutide Semi-Finished Syringe

Information on the dulaglutide semi-finished syringe was obtained from BLA 125469, eCTD Section 3.2.P.7.

Shown in Figure 1 is the primary dulaglutide container closure. This part of the review is identifying the components and specifications. The referenced master files were not evaluated as part of the device review. The safety and effectiveness properties of the semi-finished syringe will be evaluated as part of the prefilled syringe and pen injector reviews.

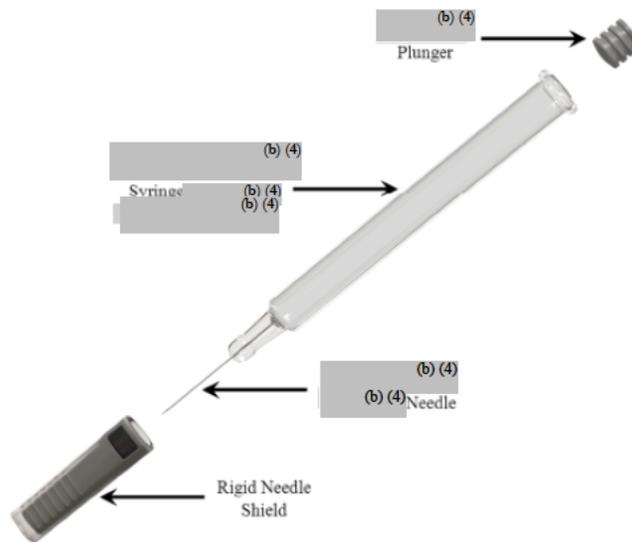


Figure 1

Component/Process	Supplier	Drug Master File Number
Syringe (b) (4)	(b) (4)	(b) (4)
Needle Shield (b) (4)		
Plunger (b) (4)		

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**Semi-Finished Syringe – Break Loose Force and Glide Force Verification Studies**

The test report is found in Section 32P5, Control of Drug Product, “32p522-compression-proc”.

Testing is described to evaluate the break loose force and glide force for the semi-finished syringe and PFS configurations. These results are applicable to the PFS and SUP.

Methodology: A load cell is used to evaluate the forces required to initiate plunger movement and to maintain plunger movement.

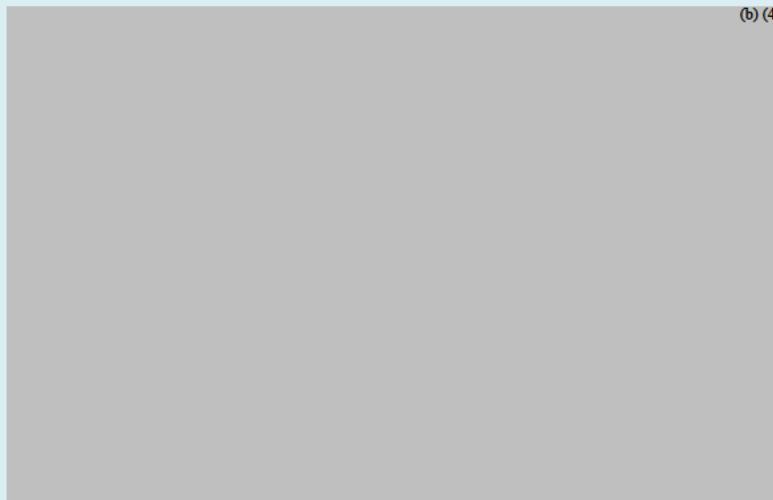


Figure 3

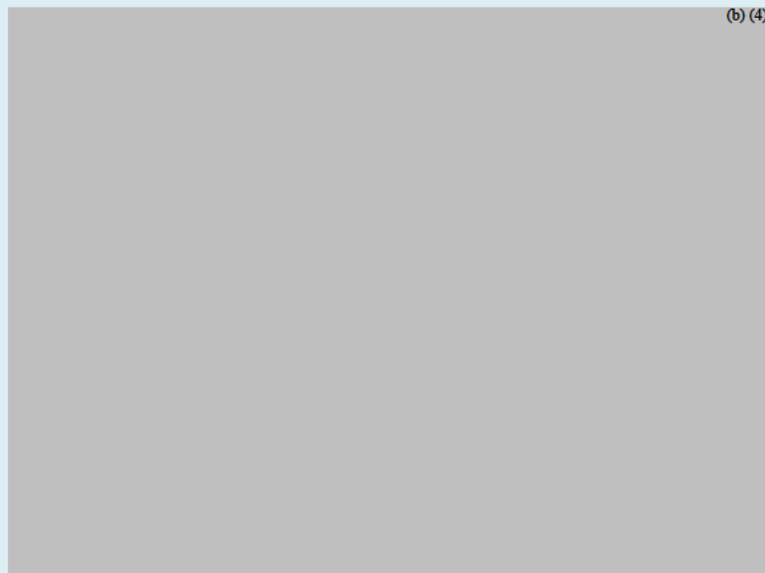


Figure 4

Figure 4 demonstrates the regions of the force response curve from which the break loose force and glide force are determined.

Results: The following results table is copied from Attachment 2 of the compression testing report.

Drug Product	BF Peak Limit (N)	GF Max Limit (N)
Dulaglutide	(b) (4)	(b) (4)

**Deficiency:** The break loose force and glide force testing for the semi-finished and prefilled syringe presentation appears to be a process capability test, rather than a design verification test. The acceptability criteria are not specified with respect to safety and effectiveness. Identify the design functional specifications on break loose force and glide force required for maintaining safe and effective drug delivery, and then provide the process capability testing demonstrating that the manufacturing process is producing the intended design.

#### D. (b) (4) Prefilled Syringe

Information on the prefilled syringe was obtained from BLA 125469, eCTD Section 3.2.R.6. The finished prefilled syringe (Figure 5) includes the semi-finished syringe (Figure 1). Added to the semi-finished syringe are the label, (b) (4) and plunger rod. This is the same injection system used in the clinical trial, with the exception of the label and colors.

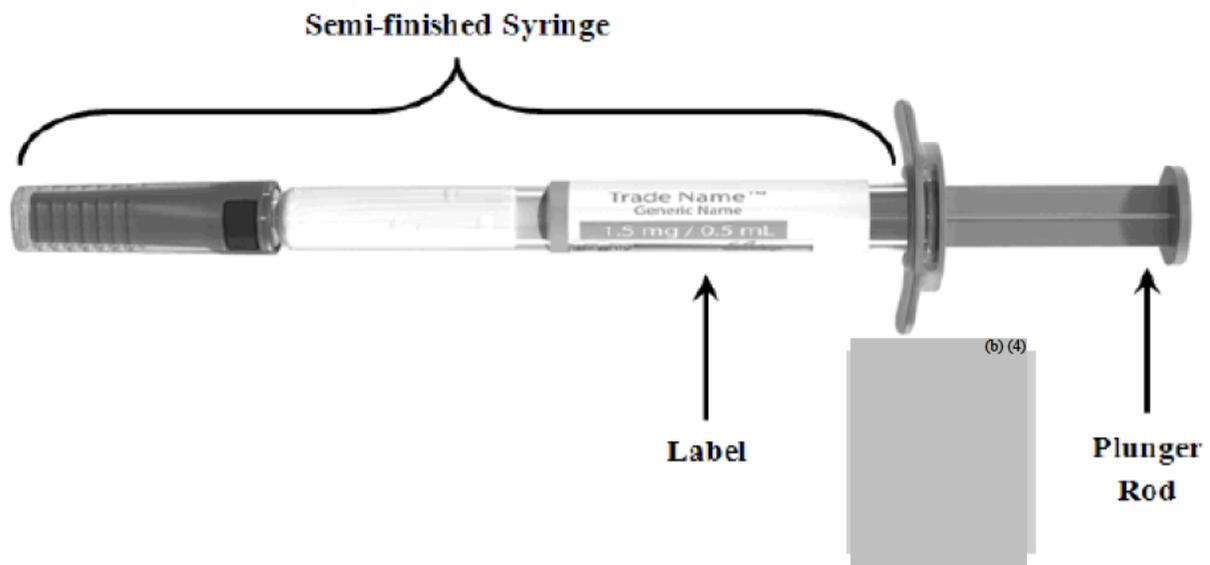


Figure 5

The prefilled syringe does not include fill level indicators or graduation marks because the product is a single dose, single use injection system. It is intended that the complete syringe volume will be injected and the empty syringe will be disposed.

The container closure (e.g., the semi-finished syringe) is filled in facilities claimed to be operating under Quality Systems in conformance to 21 CFR 210 and 21 CFR 211. Verification of this claim was not evaluated as part of the device review.

Two presentations are described: 0.75 mg / 0.5 mL and 1.5 mg / 0.5mL. Differentiation between the two presentations is by color and labeling.

Dose Strength	Color Code <sup>1</sup>
0.75 mg/0.5 mL	Yellow
1.5 mg/0.5 mL	Blue

<sup>1</sup> Plunger rod, (b) (4) and label are color coded according to the dose strength.

CDRH has developed device hazard checklists for syringes, which has been applied to this review. It is noted that many of the hazard causes are repetitive. The redundancies are included for completeness.

Table 1 – CDRH General Syringe Hazard Checklist

Device Hazard	Cause	Applicable to (b) (4) PFS		Review Comments
		Yes	No	
Delivery Error/Delay in Therapy	Device Insufficiently Patent	X		This will be evaluated as part of device non-clinical performance studies. Most likely causes of patency are manufacturing defects on the semi-finished
	Device Insufficiently Sealed to Environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Device Material Compromises	X		This is applicable, but would

	Injectable			be caused by container closure contact with the drug, which is not covered within the CDRH device review.
	Device Volume Incorrect	X		See review of delivery accuracy testing.
	Insufficient Device Dimension	X		This would cause various failure modes that could result in delivery error (e.g. plunger rod dimension does not allow complete injection). Acceptable mitigation will be addressed in the non-clinical performance studies.
	Insufficient or Compromised Visibility of Contents	X		The assembly causes do not apply to this review because the syringe is prefilled. Visibility hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Insufficient Device-User Interface	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers UI related hazards.
	Unexpected Separation of Components	X		Failure modes could occur during shipping, injection preparation, and injection. Evaluation of this hazard will be included in the CDRH review of non-clinical performance studies.
	Inappropriate or Insufficient Connection		X	This hazard relates to syringes with luer type connections, which does not apply to the PFS.
	Drug Degraded	X		This is applicable, but would be caused by container closure contact with the drug, or drug stability, which are not covered within the CDRH device review.

	Insufficient Dose/Volume Markings/Graduations		X	The sponsor notes that no markings are on the PFS.
	Incorrect Device Assembly /Preparation	X		The assembly causes do not apply to this review because the syringe is prefilled. User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Incorrect Solution Uptake		X	Syringe is prefilled. This hazard relates to drawing up the medication from a vial.
	Incorrect Device Activation	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers device activation related hazards.
	Incorrect Selection of Device	X		Device selection hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
Incorrect Therapy	Device Compromises Injectable	X		This is applicable, but would be caused by container closure contact with the drug, or drug stability, which are not covered within the CDRH device review.
	Improper Injection Site Selection	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers injection site selection related hazards.
Biological / Chemical Contamination	Device insufficiently sterile	X		Since the syringe is prefilled, the sterility issues should be addressed during drug manufacturing review /

				inspection. This is not being addressed by CDRH.
	Device Insufficiently Sealed to Environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Inappropriate or Insufficient Connection		X	This hazard relates to syringes with luer type connections, which does not apply to the PFS.
	Incorrect Device Assembly /Preparation	X		Since the syringe is prefilled, the contamination issues should be addressed during drug manufacturing review / inspection. This is not being addressed by CDRH.
	Inappropriate Device Re-use	X		Labeling indicates that the injection system is single use.
	Failure to Use Aseptic Technique	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers injection technique related hazards.
	Failure to Correctly Dispose Device	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers improper disposal related hazards.
Device allows for laceration	Device Breakage	X		The use related hazard analysis assesses the user ability to identify damaged syringe. However, the possibility of damage during injection will be evaluated during review of non-clinical performance studies.

	Device Exterior Surface Contains Sharp Edges	X		Review of injection system drawings do not identify any sharp edges, with the exception of the needle. The needle is a requirement of the injection system and mitigations have been implemented to reduce the risk associated with needle stick. Evaluation of the needle shield will be included in this review.
	Insufficient Assembly/Preparation	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers preparation related hazards.
	Inadequate Disposal	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers improper disposal related hazards.
	Insufficient Activation	X		Referred to CDRH Human Factors (see review from LCDR Quynh Nguyen). Although I have verified that the use related hazards analysis provided by the sponsor covers activation related hazards.
	Incorrect Assembly of device	X		The syringe is prefilled and presented to the user in its assembled form. Manufacturing related causes of incorrect assembly are deferred to inspection review.
Air Emboli	Device Insufficiently Sealed to Environment		X	Sponsor indicates that air emboli is not a risk to health for this combination product.
	Unexpected Separation of Components		X	
	Inappropriate or Insufficient Connection		X	

	Incorrect Device Assembly /Preparation	X	<p>The prefilled syringe IFU has a section on Commonly Asked Questions, one of which is "What if I see an air bubble in my syringe?". The response states "Air bubbles are normal. (b) (4) ."</p> <p>The human factors study identifies <i>Attempts to Eliminate Air Bubble</i> as a use error observed during the study. The cause is identified as attempting to remove air from the syringe. It was observed that in some case <u>up to 1/3 of the syringe volume was lost due to this use error.</u></p> <p>It is unclear to me that the risk assessment is adequate. I recommend that CDER medical officers evaluate if the risk assessment is valid.</p>
Particulate Emboli	Device Insufficiently Patent	X	This will be evaluated as part of device non-clinical performance studies. Most likely causes of patency are manufacturing defects on the semi-finished
	Device Insufficiently Sealed to Environment	X	Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Device Material Present within Injectable	X	This is applicable, but would be caused by container closure contact with the drug, or drug stability, which are not covered within the CDRH device review.
	Inappropriate or Insufficient Connection	X	This hazard relates to syringes with luer type connections, which does not apply to the PFS.
	Incorrect Device Assembly	X	Since the syringe is prefilled,

	/Preparation		the contamination issues should be addressed during drug manufacturing review / inspection. This is not being addressed by CDRH.
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**PFS Dose Accuracy**

The dose delivery specification for the (b) (4) PFS is 0.5mL (b) (4). Testing was conducted in accordance with ISO 11608-1:2012 - Needle-based injection systems for medical use — Requirements and test methods

Preconditioning	Testing Condition	Dose Accuracy				Pass/ Fail
		Limits (mL)	Sample Size	Target K <sup>1</sup>	Actual K	
Standard: 23±5°C/ 50±25%RH for ≥ 4 hours	23±5°C/ 50±25% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Cool: 5±3°C for ≥ 4 hours	5±3°C	(b) (4)	60	(b) (4)	(b) (4)	Pass
Warm: 40±2°C/ 50±10%RH for ≥ 4 hours	40±2°C/ 50±10% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Dry Heat: 30±2°C/ 65±5%RH for ≥ 96 hours	23±5°C/ 50±25% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Cold: 5±3°C for ≥ 96 hours	23±5°C/ 50±25% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Free Fall	23±5°C/ 50±25% RH	(b) (4)	21	(b) (4)	(b) (4)	Pass
Vibration	23±5°C/ 50±25% RH	(b) (4)	20	(b) (4)	(b) (4)	Pass

<sup>1</sup> The target k-value is, for a given sample size, the minimum actual k-value that will meet the pre-specified requirements for a quality attribute. Therefore, the actual k-value calculated for a sample must be greater than or equal to the target k-value to meet requirements.

**Design Verification**

Several design verification studies were conducted to verify specific functional requirements of the design, including forces required to initiate and maintain injection and force required to remove needle shield. Maintenance of these requirements following shipping simulation was also conducted.

**Table 3.2.R.6.3.2.2-1 Break Loose/Glide Force Testing Results**

Preconditioning	Testing Condition	Sample Size	Break Loose Force				Glide Force				
			Limit (N)	Target K	Actual K	Pass/Fail	Limit (N)	Target K	Actual K	Pass/Fail	
Standard: 23±5°C/ 50±25%RH for ≥ 4 hours	23±5°C/ 50±25% RH	35	(b) (4)				Pass	(b) (4)			

**Table 3.2.R.6.3.2.2-2 Needle Shield Removal Force Testing Results**

Preconditioning	Testing Condition	Sample Size	Needle Shield Removal Force			
			Limits (N)	Accept/Reject	# Outside Limits	Pass/Fail
Standard: 23±5°C/ 50±25%RH for ≥ 4 hours	23±5°C/ 50±25% RH	80	(b) (4)		0	Pass

**Design Verification – Shipping Studies**

To demonstrate dose accuracy, container closure integrity, and acceptable user interaction forces of the prefilled syringe following exposure to transportation hazards, testing was performed on prefilled syringes subjected to simulated and field test shipments.

(b) (4)

All dose accuracy measurements following the shipping studies met the requirement for 95% confidence that 95.0% of the doses delivered fell within the (b) (4) specification range.

**Table 3.2.R.6.3.3-1 Dose Accuracy Testing Results Following Shipping**

Shipment Type	Testing Condition	Sample Size	Dose Accuracy			
			Limits (mL)	Target K	Actual K	Pass/Fail
Simulation	23±5°C/ 50±25% RH	13	(b) (4)			Pass
Field Test			(b) (4)			Pass

**Table 3.2.R.6.3.3-2 Container Closure Integrity Test Results Following Shipping**

Shipment Type	Test Method	Quantity Tested	Results
Simulation	(b) (4)	20	Pass <sup>1</sup>
		20	Pass
Field Test		20	Pass <sup>1</sup>
		20	Pass

<sup>1</sup> Positive controls from testing of the batch showed (b) (4) acceptance criteria.

**Table 3.2.R.6.3.3-3 Break Loose/Glide Force Testing Results Following Shipping**

Shipment Type	Testing Condition	Sample Size	Break Loose Force				Glide Force			
			Limit (N)	Target K	Actual K	Pass/Fail	Limit (N)	Target K	Actual K	Pass/Fail
Simulation	23±5°C/ 50±25% RH	13	(b) (4)			Pass	(b) (4)			Pass
Field Test			(b) (4)			Pass	(b) (4)			Pass

**Table 3.2.R.6.3.3-4 Needle Shield Removal Force Testing Results Following Shipping**

Shipment Type	Testing Condition	Sample Size	Needle Shield Removal Force			
			Limits (N)	Accept/Reject	# Outside Limits	Pass/Fail
Simulation	23±5°C/ 50±25% RH	43	(b) (4)	0/1	0	Pass
Field Test			0		Pass	

**Shelf Life**

Shelf life testing of the SUP is contained in Section 3.2.P.8.3.2 – supporting stability.

Testing was conducted according to the following protocol (b) (4)

**Table 3.2.P.8.3.2.1.3-4 (continued) Supporting Stability Protocol for the Drug Product Packaged in Prefilled Syringes, Process Validation Batches**

Analytical Property	Method Type	Storage Conditions	I <sup>1</sup>	Months										
				0.5	1	2	3	6	12	18	T <sub>exp</sub>	24	30	
Functionality: Break Loose / Glide Force	Compression	2-8°C	-	-	-	X	X	X	X	X	X	X	X	X
		25°C/60% RH	I	-	X	-	X	X	-	-	-	-	-	-
		30°C/65% RH	-	X	X	X	-	-	-	-	-	-	-	-
Visual and Functional Inspection	Visual Inspection and Manual Operation	2-8°C	-	-	-	X	X	X	X	X	X	X	X	
		25°C/60% RH	I	-	X	X	X	-	-	-	-	-	-	
		30°C/65% RH	-	X	X	-	-	-	-	-	-	-	-	
Container Closure Integrity	Dye Ingress	2-8°C	-	-	-	-	-	-	X	-	-	X	X	

Abbreviation: I = Initial  
<sup>1</sup> The initial time point is considered to be (b) (4)  
 T<sub>exp</sub> = additional time point added at the batch expiration if a scheduled time point is not within 30 days of date of manufacture.

**Results**

**Table 3.2.P.8.3.2.1.6.2-2 (continued) Stability Results for Validation Batch C038888B 1.5 mg/0.5mL, Prefilled Syringe**

Analytical Property	Acceptance Criteria <sup>1</sup>	Method	Condition	Time Point									
				Initial	2 Weeks	1 Month	2 Months	3 Months	6 Months				
<b>Other Tests</b>													
Polysorbate 80 Concentration	(b) (4)	(b) (4)	2-8°C										
			25°C/60% RH										
			30°C/65% RH										
Functionality: Break Loose Force	(b) (4)	Compression	2-8°C										
25°C/60% RH													
30°C/65% RH													
Functionality: Glide Force	(b) (4)	Compression	2-8°C										
25°C/60% RH													
30°C/65% RH													
Visual and Functional Inspection	(b) (4)	Visual Inspection and Manual Operation	2-8°C										
25°C/60% RH													
30°C/65% RH													

N/A = Not Applicable  
<sup>1</sup> Acceptance criteria listed are those in effect at the start of the stability study.  
<sup>2</sup> Samples not tested due to shipping error to test laboratory.

**Biological Safety**

Biocompatibility and sterility of the drug and container closure are deferred to CDER review.

**E. (b) (4) Pen Injector**

The single-use pen includes the dulaglutide semi-finished syringe. The single-use pen is intended to enable patients, caregivers or Health Care Professionals (HCP) to administer a single dose, subcutaneous injection of dulaglutide. The single-use pen Label provides information for drug product and dosage form as well as covering the mechanical apparatus within the single-use pen. The activation end incorporates a lock feature to prevent unintentional activation and an Injection Button to start the injection sequence. The injection end of the single-use pen incorporates a Base Cap for needle shield removal and Clear Base for stable positioning at injection site with 360 degree viewing of drug product.

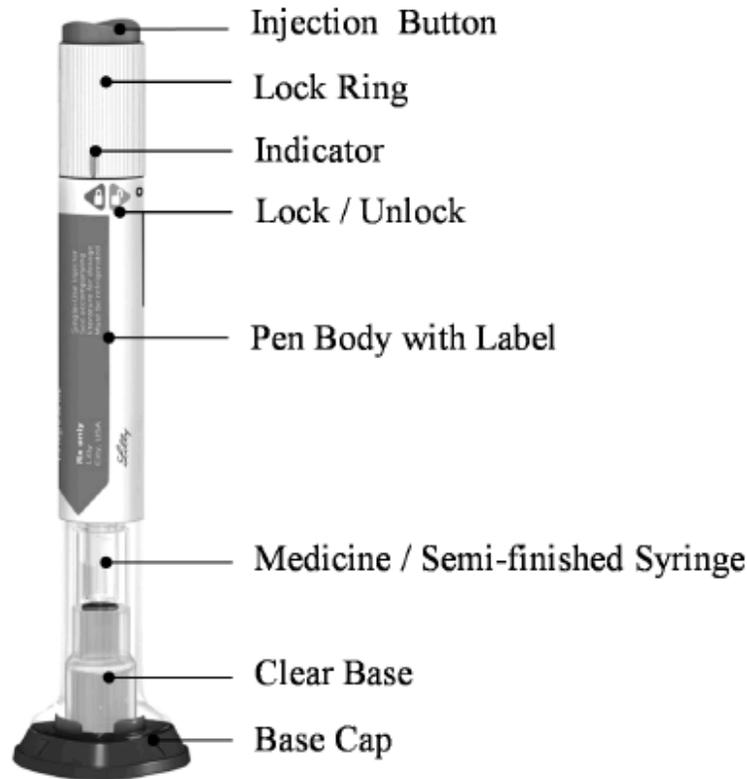


Figure 6

Dulaglutide injection is supplied as either 0.75 mg/0.5 ml or 1.5 mg/0.5 ml, and is a sterile, non-preserved solution for subcutaneous injection. The following single-use pens are available:

- Single-use pen, 0.75 mg - Each single-dose, prefilled single-use pen contains 0.75 mg of dulaglutide per 0.5 mL of solution.

BLA 125469

Eli Lilly

Prefilled Syringe and Pen Injector for injection of (b) (4)

Device Engineering Consult

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- Single-use pen, 1.5 mg - Each single-dose, prefilled single-use pen contains 1.5 mg of dulaglutide per 0.5 mL of solution.

The single-use pen is prefilled with dulaglutide and is designed to deliver the entire dose in a single injection.

(b) (4)

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The (b) (4) Pen Injector is available in dose strength presentations: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL. Each presentation is color coded according to the following table.

**Table 3.2.R.5.2.8.2-1 Dulaglutide Injection Single-use Pen Dose Strength Color Coding**

Dose Strength	Color Code <sup>1</sup>
0.75 mg/0.5 mL	Yellow
1.5 mg/0.5 mL	Blue

<sup>1</sup> Single-use Pen label is color coded according to the dose strength.

CDRH has developed device hazard checklists for pen injectors, which has been applied to this review. It is noted that many of the hazard causes are repetitive. The redundancies are included for completeness.

**Table 2 – CDRH General Pen Injector Hazard Checklist**

Device Hazard	Cause	Applicable to Pen		Review Comments
		Yes	No	
Delivery Error/Delay in Therapy	Device fluid path occlusion	X		Likely sources are manufacturing defect on the needle, needle / syringe connection, or particulate formation in the drug.
	Device alters/adds/retains contents	X		This is related to the leachable / extractables emanating from the semi-finished syringe. Review of these issues are deferred to CDER.
	Insufficient visibility of contents	X		Visibility hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Incomplete drug delivery	X		This is a hazard most likely related to component failure, component interaction failure, or use error.

	Unexpected separation of components	X		Failure modes could occur during shipping, injection preparation, and injection. Evaluation of this hazard will be included in the CDRH review of non-clinical performance studies.
	Excessive drug delivery		X	This is applicable to multi-dose injectors.
	Component failure	X		Sponsor references FMEA. Results will be evaluated.
	Device insufficiently sealed to environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Device does not indicate amount of drug delivered/not delivered		X	This is not applicable to single-dose injectors.
	Insufficient dose/volume markings/graduation markings		X	This is not applicable to this single-dose injector.
	Incorrect device preparation	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Insufficient device activation	X		User activation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). Mechanical causes are covered in this review.
	Injection initiates prior to needle reaching the correct tissue depth of penetration.	X		The sponsor has identified (b) (4) specification at which the injection will commence. This is covered in the review.
	Device used after expiration date	X		This is deferred to the CDRH human factors review. The labeling was verified to contain an expiration date.  Also implicit in this hazard is that the combination product is safe and effective for use at or before the expiry. Review of shelf life information for the

				device verifies that the labeled storage conditions have been verified.
	Incorrect Selection of Device	X		Device selection hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Incorrect Injection Site	X		Injection site selection hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen).
Incorrect Therapy	Device Compromises Injectable	X		This is related to leachables causing adverse impact to the drug. Review of this issue is deferred to CDER.
	Improper Injection Site Selection	X		Injection site selection hazards are deferred to CDRH human factors (see review from LCDR Quynh Nguyen).
Biological / Chemical Contamination	Device insufficiently sterile	X		This is important as it relates to the semi-finished prefilled syringe, which is being manufactured under drug manufacturing regulations. Therefore, review of this issue is deferred to CDER.
	Leachables released from device	X		Review of this issue is deferred to CDER.
	Inappropriate Storage	X		Shelf life issues related to the functionality of the pen injector have been adequately addressed by the sponsor.
	Device Insufficiently Sealed to Environment	X		Most likely this is related to defects introduced during manufacture (not covered in this review) or during shipping / transport (covered).
	Inappropriate or Insufficient Connection	X		As it relates to internal components properly interfacing / connecting to each other, this hazard will be covered in this review.
	Incorrect Device Assembly	X		User preparation related

	/Preparation			causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Inappropriate Device Re-use	X		The device is labeled as single-use. Review will cover any additional mitigations to prevent re-use.
	Failure to Use Aseptic Technique	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Failure to Correctly Dispose Device	X		Disposal related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen).
Device allows for laceration	Device Body Breakage	X		These hazards are covered in this review.
	Needle Fracture / Remains Embedded in Subcutaneous Tissue	X		Needle fracture hazards will be covered in this review.
	Device Exterior Surface Contains Sharp Edges	X		Analysis of drawings does not identify any sharp edges.
	Insufficient Assembly/Preparation	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
	Inadequate Disposal	X		Disposal related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). This review will cover any mechanical hazards relating to needle retraction features.
	Insufficient Activation	X		User activation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). Mechanical activation hazards are covered in this review.

	Incorrect Assembly of device	X		User preparation related causes are deferred to CDRH human factors (see review from LCDR Quynh Nguyen). I confirmed with LCDR Nguyen that the study covered this hazard.
Air Emboli	Device Insufficiently Sealed to Environment		X	Sponsor indicates that air emboli is not a risk to health for this combination product.
	Unexpected Separation of Components		X	
	Inappropriate or Insufficient Connection		X	
	Incorrect Device Assembly /Preparation		X	
Particulate Emboli	Particulate released from device. Device Material Present within Injectable	X		The source would be the container closure. Review is deferred to CDER CMC reviewers.
	Incorrect Device Assembly /Preparation	X		As it relates to internal components properly interfacing / connecting to each other, this hazard will be covered in this review.

The following tables identify design verification studies and results for the SUP.

<p>(b) (4) <b>Pen Injector – Dose Accuracy</b></p> <p>The dose delivery specification for the (b) (4) Pen Injector is 0.5mL (b) (4) Testing was conducted in accordance with ISO 11608-1:2012 - Needle-based injection systems for medical use — Requirements and test methods.</p>
---

**Table 3.2.R.5.3.2.1.1-1 ISO 11608-1 Dose Accuracy Testing Results**

Preconditioning	Testing Condition	Dose Accuracy				
		Limits	Sample Size	Target K <sup>1</sup>	Actual K	Pass/Fail
Standard: 23±5°C/ 50±25%RH for ≥ 4 hours	23±5°C/ 50±25% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Cool: 5±3°C for ≥ 4 hours	5±3°C	(b) (4)	60	(b) (4)	(b) (4)	Pass
Warm: 40±2°C/ 50±10%RH for ≥ 4 hours	40±2°C/ 50±10% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Cold Storage: 5±3°C for ≥ 96 hours	23±5°C/ 50±25% RH	(b) (4)	60	(b) (4)	(b) (4)	Pass
Free Fall	23±5°C/ 50±25% RH	(b) (4)	21	(b) (4)	(b) (4)	Pass
Vibration	23±5°C/ 50±25% RH	(b) (4)	20	(b) (4)	(b) (4)	Pass

<sup>1</sup> The target k-value is, for a given sample size, the minimum actual k-value that will meet the pre-specified requirements for a quality attribute. Therefore, the actual k-value calculated for a sample must be greater than or equal to the target k-value to meet requirements.

**Injection Depth**

**Table 3.2.R.5.3.2.1.2-1 Exposed Needle Distance Test Results**

Exposed Needle Distance	Limits	Sample Size	Target K	Actual K	Pass / Fail
Minimum Distance	(b) (4)	25	(b) (4)	(b) (4)	Pass
Maximum Distance	(b) (4)		(b) (4)	(b) (4)	Pass

**User Interaction Forces and Injection Time**

**Table 3.2.R.5.3.2.2-1 User Interaction Forces and Injection Time Test Results**

Test	Analytical Procedure	Acceptance Criteria	Sample Size	Target K	Actual K	Pass/Fail
		(b) (4)	60		(b) (4)	Pass
			60			Pass
			60			Pass
			60			Pass
			60			Pass

<sup>1</sup> Acceptance criteria for (b) (4) is based on an average. Actual mean force is (b) (4)

**Shipping Studies**

**Table 3.2.R.5.3.3-1 Leakage and Dose Accuracy Test Results following Pressure Change**

Test	Sample Size (n)	Acceptance Criteria/Limits	Average mL	Target K	Actual K	Pass/Fail
Visual Inspection for Leakage	25	(b) (4)			(b) (4)	Pass
Dose Accuracy						Pass
						Pass

To demonstrate visual and functional performance of SUPs and secondary packaging following exposure to shipping hazards, visual and functional inspections were performed on packaged product subjected to a simulated shipment. The simulated shipping study included the following:

- (b) (4)
- (b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

**Table 3.2.R.5.3.3-5 Dose Accuracy and Injection Process Time Test Results Following Shipping**

Shipment Type	Test / Limits	Sample Size	Test Results			Pass/Fail
Simulation	(b) (4)	35	Average (mL)	$p^*_{\text{required}}^1$	p-hat	
			(b) (4)			Pass
						Pass
Field Test	(b) (4)	35	(b) (4)			Pass
						Pass
						Pass

<sup>1</sup> The  $p^*$  is, for a given sample size, the maximum estimated proportion of units outside of specifications that will meet the pre-specified requirements for a quality attribute. The estimated proportion of units outside of specifications is p-hat. Therefore, the p-hat for a sample must be less than or equal to the  $p^*$  to meet requirements.

**Shelf Life**

Shelf life testing of the SUP is contained in Section 3.2.P.8.3.2 – supporting stability.

Testing was conducted according to the following protocol (b) (4)

Table 3.2.P.8.3.2.1.3-1 (continued) Supporting Stability Protocol for the Drug Product  
Packaged in Single Use Pens, (b) (4)

Analytical Property	Method Type (b) (4)	Storage Conditions	Months							
			I <sup>1</sup>	0.25	0.5	1	3	6	9	12
Particulate Matter (b) (4)		2-8°C	-	-	-	-	X	-	X	
		30°C/75% RH	I	X	X	X	-	-	-	-
Color		2-8°C	I	-	-	-	-	X	X	X
		30°C/75% RH		X	X	X	-	-	-	-
Clarity		2-8°C	I	-	-	-	-	X	X	X
		30°C/75% RH		X	X	X	-	-	-	-
Polysorbate 80 Concentration		2-8°C	I	-	-	-	-	X	-	X
		30°C/75% RH		X	X	X	-	-	-	-
Dose Accuracy		2-8°C	I	-	-	-	X	X	X	X
		30°C/75% RH		X	X	X	-	-	-	-
Visual and Functional Inspection		2-8°C	I	-	-	-	X	X	X	X
		30°C/75% RH		X	X	X	-	-	-	-
Container Closure Integrity		2-8°C	-	-	-	X	-	-	-	X

<sup>1</sup> The initial time point is considered to be (b) (4)

**Results:**

Table 3.2.P.8.3.2.1.6.1-2 (continued) Stability Results for (b) (4) Validation Batch C156963C  
0.75 mg/0.5mL, Single Use Pen

Analytical Property	Acceptance Criteria <sup>1</sup>	Method	Condition	Time Point (Weeks)		
				Initial	1	2
<b>Other Tests</b>						
Color	(b) (4)	(b) (4)	2-8°C	(b) (4)	(b) (4)	(b) (4)
			30°C/75% RH			
Clarity			2-8°C			
			30°C/75% RH			
Polysorbate 80 Concentration			2-8°C			
			30°C/75% RH			
Dose Accuracy			2-8°C			
	30°C/75% RH					
Visual and Functional Inspection	2-8°C					
	30°C/75% RH					
Container Closure Integrity	2-8°C					

N/A = Not Applicable

<sup>1</sup> Acceptance criteria listed are those in effect at the start of the stability study.

<sup>2</sup> Two initial time point samples were inadvertently analyzed for this test.

<sup>3</sup> Sample tested at 1 month of age.

**Labeled Storage Conditions**

The proposed storage condition for dulaglutide injection is refrigerated (2-8°C). The proposed storage time and condition for patient in use is 14 days at ambient temperature (not more than 30°C). Dulaglutide injection should be stored protected from excessive heat and from direct sunlight.

**Biological Safety**

Biocompatibility and sterility of the drug and container closure are deferred to CDER review.

Biocompatibility of the pen body materials are addressed in Section 3.2.R.5.3.1.

**Table 3.2.R.5.3.1-1 Patient Exposure Materials**

Patient Contacting Component	Material of Construction
Injection Button	(b) (4)
Lock Ring	(b) (4)
Base Cap	(b) (4)
Body Lower	(b) (4)
Baseplate	(b) (4)

The assessment provided by the sponsor concluded the safety of the identified components for use as a non-drug product contact materials of construction is demonstrated by a safe history of use in consumer products. These consumer product materials have substantial equivalence to the single-use pen in terms of frequency and extent of dermal contact under normal use conditions. Furthermore, published material testing, certifications, and material use in predicate devices provide additional justification the materials are safe for dermal contact. The evaluated materials of construction are consistent with the requirements of ISO 10993-1, pose no risk to patient or user safety, and no additional support of safety is required.

**IV. Review Comments and Recommended Deficiencies**

Note to CDER

The prefilled syringe IFU has a section on Commonly Asked Questions, one of which is “What if I see an air bubble in my syringe?”. The response states “Air bubbles are normal.” (b) (4)

The human factors study identifies *Attempts to Eliminate Air Bubble* as a use error observed during the study. The cause is identified as attempting to remove air from the syringe. It was observed that in some case up to 1/3 of the syringe volume was lost due to this use error.

It is unclear to me that the risk assessment is adequate. I recommend that CDER evaluate if the risk assessment is valid.

Deficiencies

1. We have completed our review of the documentation submitted in support of the (b) (4) single use pen. During our review we evaluated the documentation to determine if hazards associated

with the use of this device are adequately addressed. There are hazardous situations that do not appear to be explicitly addressed in your submission:

Hazardous Situation	
Delivery Error	Device fluid path occlusion
	Incomplete drug delivery
	Unexpected separation of components
	Component failure
	Device insufficiently sealed to environment
	Insufficient / inadequate device activation
	Injection initiates prior to needle reaching the correct tissue depth of penetration.
Contamination	Device Reuse
Trauma	Device Body Breakage
	Needle Fracture / Remains Embedded in Subcutaneous Tissue
	Unexpected separation of components

Please provide a system level hazard analysis (e.g. fault tree analysis) identifying the causes of these hazardous situations for the (b) (4) single use pen injector. For each identified cause, provide the following:

- a. Describe the control method for each identified cause.
  - b. For each cause, provide an argument justifying the adequacy of the control to address the respective system hazard.
  - c. Provide evidence verifying the control method adequately addresses the respective cause / hazard.
2. Many of the design verification studies present the results in the following format:

Test Characteristic	Acceptance Criteria	Sample Size	Target K	Actual K	Pass / Fail
---------------------	---------------------	-------------	----------	----------	-------------

We are familiar with the use of tolerance limit factors when presenting design verification studies for pen injectors, and other delivery devices. However, the presentation of design verification results in your submission is not well understood. For example, we would generally expect to see results in the following format:

Test Characteristic	Acceptance Criteria	Sample Size	Mean, $\bar{x}$	Standard deviation, $\pm\sigma$	Lower / Upper Spec Limit, $x \pm k\sigma$	Pass / Fail
---------------------	---------------------	-------------	-----------------	---------------------------------	---	-------------

Please provide the derivation of tolerance limit factor, k, to the Target K value and explain how this corresponds to the device performance. Alternatively, reformat the results into the expected format, as specified in the second table.

3. There does not appear to be any performance evaluation on the needle to verify that the mechanical strength properties, patency, etc. are reliably achieved. Additionally, there does not appear to be information regarding manufacture of the needle and assurance that the manufacturing process reliably produces a needle that conforms to its specifications. Needle based hazards may be covered as part of the response to the hazardous situations, which is only related to the single use pen injector. However, please be sure to update the submission with specific information regarding the safe and effective use of the needle component of the prefilled syringe and single use pen injector.
4. Section 3.2.P.5 includes specifications for the device constituents. Many of the device acceptance criteria are identified only as "Pass". This is not sufficient. Update the specifications with the specific acceptability criteria that will be applied, as verified and validated. Additionally, the list of specifications is not complete. For example, specifications for injection depth, activation force, needle retraction time, injection force, locking mechanism override force, time between injection activation and injection initiation, etc. are not specified. Provide a complete list of device functional specifications with the corresponding acceptability criteria.
5. The break loose force and glide force testing (Section 3.2.P.5, Control of Drug Product, "32p522-compression-proc.pdf) for the semi-finished and prefilled syringe presentation appears to be a process capability test, rather than a design verification test. The acceptability criteria are not specified with respect to safety and effectiveness. Identify the design functional specifications on break loose force and glide force required for maintaining safe and effective drug delivery, and then provide the process capability testing demonstrating that the manufacturing process is producing the intended design.
6. The batch analysis results (Section 3.2.P.5.4) identifies tests, acceptance criteria, and results for the single use pen, prefilled syringe, and semi-finished syringe. Please address the following issues related to the device testing:
  - a. The visual inspection and functional inspection (manual operation) tests are not clearly described such that we understand what the tests entail. Further, the acceptance criteria are stated as "pass", which is not adequate. Update the table to include specifics of the visual and functional inspection tests and identify specific acceptance criteria.
  - b. Break loose force and glide force acceptance criteria are listed as an upper bound (e.g. NMT (b) (4) and NMT (b) (4), respectively) and no minimum force requirements are specified. (b) (4)  

Identify a lower limit on the force requirements for initiating and maintaining an injection and provide a justification for the acceptability criteria.
7. The shipping simulation testing results for the single use pen indicates on major defect following testing (Table 3.2.R.5.3.3-6). Please describe the observed defect, describe the impact to the patient from the defect and provide a risk assessment.
8. The (b) (4) single use pen instructions for use references the Medication Guide for complete information about proper storage; however, the Medication Guide does not appear to include any storage information. Please correct the discrepancy.

BLA 125469

Eli Lilly

Prefilled Syringe and Pen Injector for injection of (b) (4)

Device Engineering Consult

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## V. Decision Recommendation

I recommend conveying the deficiencies to the sponsor.

<b>Digital Signature Concurrence Table</b>	
Reviewer	
Supervisor	

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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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ABOLADE ADEOLU  
03/12/2014

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
BLA# 125469	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: dulaglutide Dosage Form: Injection Strengths: 1.5 mg/0.5 mL		
Applicant: Eli Lilly and Company Agent for Applicant (if applicable): N/A		
Date of Application: September 17, 2013 Date of Receipt: September 18, 2013 Date clock started after UN:		
PDUFA Goal Date: September 18, 2014		Action Goal Date (if different):
Filing Date: November 17, 2013 (Sunday)		Date of Filing Meeting: October 31, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>                      and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	Standard   <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number: 070930				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Standard review
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application:  Paid			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:  Not in arrears			
<b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	BLA
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?  <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>			X	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>  <b>If yes, please list below:</b>			X	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>		X		

<a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDA/NDA efficacy supplements only</i> )  <b>If yes</b> , # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDA only</i> )?			X	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	All electronic  CTD			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDA/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		X		
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>			X	
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup>

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	X			<i>OPDP, OMP, DMEPA, and CDRH-9.23.13</i>
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> November 10, 2009  <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> July 9, 2013  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** October 31, 2013

**BLA #:** 125469

**PROPRIETARY NAME:** (b) (4)

**ESTABLISHED/PROPER NAME:** dulaglutide

**DOSAGE FORM/STRENGTH:** 1.5 mg/ 0.5 mL

**APPLICANT:** Eli Lilly and Company

**PROPOSED INDICATION:** adjunct to diet and exercise to improve glycemic control in adults with T2DM

**BACKGROUND:** Dulaglutide is a glucagon-like peptide GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Dulaglutide is a sterile product consisting of 1.5 mg/0.5 mL prefilled syringe (PFS) and 1.5 mg/0.5 mL single use pen (SUP). A dose of 1.5 mg dulaglutide is to be administered subcutaneously once weekly at any time of the day, with or without meals.

This application will be reviewed under the PDUFA V program, and the PDUFA goal date is September 18, 2014.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Abolade (Bola) Adeolu	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Ali Mohamadi		Y
Clinical	Reviewer:	Karim Calis	Y
	TL:	Ali Mohamadi	Y
Social Scientist Review (for OTC	Reviewer:		

<i>products)</i>			
	TL:		
OTC Labeling Review ( <i>for OTC products)</i>	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products)</i>	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sang Chung	Y
	TL:	Lokesh Jain	Y
Biostatistics	Reviewer:	Bradley McEvoy	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tim Hummer	Y
	TL:	Karen Davis-Bruno	Y
Statistics (safety)	Reviewer:	Janelle Charles	Y
	TL:	Matt Soukup	Y
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	Joel Welch	Y
	TL:	Laurie Graham	Y
Product Quality (CMC)	Reviewer:	Joel Welch	Y
	TL:	Laurie Graham	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Bo Chi (drug substance) Colleen Thomas (drug product)	N
	TL:	Patricia Hughes	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Cynthia Kleppinger	Y
	TL:	Janice Pohlman	Y
OSE/DMEPA (proprietary name)	Reviewer:	Sara Vee	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	Y
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p>Not Applicable</p>
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<p>YES</p>
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<p>Not Applicable</p>
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<p>FILE</p>
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<p>YES</p>

<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	TBD
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	Not Applicable
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	Not Applicable
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	Not Applicable
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	FILE Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	TBD
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	FILE
<p><b>NONCLINICAL</b></p>	FILE

<p><b>(PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	FILE
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	FILE
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	YES
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	Not Applicable
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	YES  YES

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p>FILE</p>
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p>NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p>YES</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p>YES</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p>YES</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b></p>	

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): **February 13, 2014**

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:** Wrap-Up Meeting: **July 24, 2014**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p>Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p>Standard Review</p>

**ACTIONS ITEMS**

X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
N/A	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
X	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
X	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the

	completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
X	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

-----  
**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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ABOLADE ADEOLU  
11/13/2013

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** BLA 125469

**Application Type:** New BLA

**Name of Drug:** (b) (4) (dulaglutide [rDNA origin] injection)

**Applicant:** Eli Lilly and Company

**Submission Date:** September 17, 2013

**Receipt Date:** September 18, 2013

## 1.0 Regulatory History and Applicant's Main Proposals

Application for dulaglutide [rDNA origin] injection) was received on September 18, 2013. Dulaglutide is a glucagon-like peptide GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Dulaglutide is a sterile product consisting of 1.5 mg/0.5 mL prefilled syringe (PFS) and 1.5 mg/0.5 mL single use pen (SUP). A dose of 1.5 mg dulaglutide is to be administered subcutaneously once weekly at any time of the day, with or without meals.

This application will be reviewed under the PDUFA V program, and the PDUFA goal date is September 18, 2014.

## 2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 2.0 Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

## 4.0 Appendix

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### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

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### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

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Comment:

**YES**

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

Comment:

#### Initial U.S. Approval

**YES**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

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### Boxed Warning

- YES** 12. All text must be **bolded**.  
Comment:
- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).  
Comment:
- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.  
Comment:
- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)  
Comment:
- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).  
Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.  
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.  
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.  
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
Comment:

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”  
Comment:

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### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

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- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.  
*Comment:*
- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.  
*Comment:*
- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
*Comment:*
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
*Comment:*
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
*Comment:*
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”  
*Comment:*
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## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
*Comment:*
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
*Comment:*
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>

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8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- YES** 42. All text is **bolded**.

**Comment:**

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

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**N/A** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

### Adverse Reactions

**YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

**N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### Patient Counseling Information

**YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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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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ABOLADE ADEOLU  
11/13/2013