

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205692Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205692	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Basaglar Established/Proper Name: insulin glargine Dosage Form: injection Strengths: 100 units/mL		
Applicant: Eli Lilly		
Date of Receipt: October 16, 2015		
PDUFA Goal Date: December 16, 2015	Action Goal Date (if different):	
RPM: Callie Cappel-Lynch		
Proposed Indication(s): to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 21081 Lantus	FDA's previous finding of safety and effectiveness

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor conducted BA/BE studies. Randomized Phase 3 studies were also conducted against the referenced product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Lantus	21081	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a product that has zinc oxide while Lantus has zinc chloride, with the same zinc ion content for both products.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “**NO**” to (a) proceed to question #11.

If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 7476652, 7713930, 7918833, 8512297, 8556864, 8603044, 8679069, 8992486, 9011391

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 7476652, 7713930, 7918833, 8603044, 8512297, 8556864, 8679069, 8992486, 9011391

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): December 19 and 20, 2013, January 24 and 27, 2014, May 15 and 27, 2014, October 19 and 20, 2015

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Note: The amendment dated February 21, 2014, states:

“Lilly has been notified that Sanofi-Aventis U.S. LLC and Sanofi-Aventis Deutschland GMBH (collectively “Sanofi”) filed a patent infringement suit on January 30, 2014 against Lilly in response to receiving notice from Lilly according to 21 CFR 314.52 about this 505(b)(2) NDA 205,692 being accepted for filing by FDA. Sanofi’s LANUS® and LANTUS® SoloSTAR® are the reference listed drugs for NDA 205,692. This general correspondence is to inform FDA of this event.”

Resubmission received on October 16, 2015, states:

“The matter of Sanofi-Aventis U.S. LLC, Sanofi- Aventis Deutschland GMBH v. Eli Lilly and Company, District Court of Delaware, Cause No. 14-113-RGA-MPT, is the subject of a Consent Judgment and Order of Injunction that by its effect allows FDA to take final approval action at this time regarding NDA 205692. The Consent Judgment, a copy of which is attached, states: “This Consent Judgment constitutes a ‘consent decree’ pursuant to 21 U.S.C. § 355(c)(3)(C)(i)(II), such that Final Approval of Eli Lilly’s NDA No. 205-692 under 21 U.S.C. § 355(b)(2) may be granted on the date that this Consent Judgment is entered by the Court.” The Consent Judgment was signed and entered by the Court on 28 September 2015.”

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

/s/

CALLIE C CAPPEL-LYNCH
12/16/2015

505(b)(2) ASSESSMENT

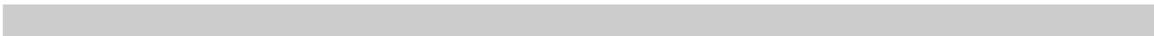
Application Information		
NDA # 205692	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Basaglar Established/Proper Name: insulin glargine Dosage Form: injection Strengths: 100 units/mL		
Applicant: Eli Lilly		
Date of Receipt: October 18, 2013		
PDUFA Goal Date: August 18, 2014		Action Goal Date (if different): August 18, 2014
RPM: Callie Cappel-Lynch		
Proposed Indication(s): to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 21081 Lantus	FDA's previous finding of safety and effectiveness

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor conducted BA/BE studies. Randomized Phase 3 studies were also conducted against the referenced product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Lantus	21081	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.
If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?
YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a product that has zinc oxide while Lantus has zinc chloride, with the same zinc ion content for both products.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5656722, 7476652, 7713930, 7918833, 8512297, 8556864, 8603044, 8679069

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 5656722

Expiry date(s): 2/12/15

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 7476652, 7713930, 7918833, 8603044, 8512297, 8556864, 8679069

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *December 19 and 20, 2013, January 24 and 27, 2014, May 15 and 27, 2014*

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Note: The amendment dated February 21, 2014, states:

"Lilly has been notified that Sanofi-Aventis U.S. LLC and Sanofi-Aventis Deutschland GMBH (collectively "Sanofi") filed a patent infringement suit on January 30, 2014 against Lilly in response to receiving notice from Lilly according to 21 CFR 314.52 about this 505(b)(2) NDA 205,692 being accepted

for filing by FDA. Sanofi's LANUS® and LANTUS® SoloSTAR® are the reference listed drugs for NDA 205,692. This general correspondence is to inform FDA of this event.”

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

/s/

CALLIE C CAPPEL-LYNCH
08/18/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing and Quality

Respiratory, E/N/T, General Hospital, and Ophthalmic Devices Branch

DATE: August 11, 2014

TO: Callie Cappel-Lynch, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, CDER, WO22-3362
Callie.CappelLynch@fda.hhs.gov

Julie Van der Waag, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, CDER, WO22-3350
Julie.VanderWaag@fda.hhs.gov

Steven Hertz, Division of Good Manufacturing Practices A, Office of Manufacturing and Product Quality, Office of Compliance, CDER, WO51-4222
Steven.Hertz@fda.hhs.gov

Office of combination products at combination@fda.gov

From: Francisco Vicenty, REGOD, DMQ, OC, CDRH, OMPT. WO-66, Room 2642

Applicant: Eli Lilly & Co
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285
FEI# 1819470

Application # NDA 205692

Product Name: (b) (4) KwikPen (insulin glargine rDNA Origin)

Consult Reassess the need for medical device inspections for the facilities
Instructions: identified in the review.

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205692, to reassess the need for medical device inspections at the manufacturing sites identified in the submission given the additional inspection history recently provided.

(b) (4) (insulin glargine rDNA origin) is a long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. It is administered as a subcutaneous injection and made in strength of 100 units per ml available in a 3 ml cartridge sealed in a pre-filled pen injector.

Application documents evaluation

No additional review of the documentation was performed during this reassessment. That documentation was reviewed as part of the original consult completed on November 21, 2013.

Regulatory history evaluation

After reviewing the application, the Eli Lilly & Co site located at Lilly Corporate Center, Drop Code (b) (4) Indianapolis, IN (FEI# 1819470), was identified as a facility subjected to applicable Medical Device Regulations under 21 CFR part 820.

An analysis of the firm's inspection history over the past 2 years showed that an inspection under the Medical Device regulation was conducted on April 15-19, 2013. The inspection covered a level II device inspection for the Humalog KwikPen and was classified VAI. A two observation 483 was issued regarding no documentation of rework and reevaluation activities in the (b) (4) and inadequate establishment of procedures to control non-conforming products.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 205692 and has the following recommendations:

Application NDA 205692 for the (b) (4) KwikPen is approvable from the perspective of

the Medical Device Regulations. The desk review of the application for compliance with the Medical Device Regulations showed no deficiencies, and no facilities need to be inspected with regards to the Medical Devices Regulations prior to approval.

Francisco Vicenty -S
2014.08.12 00:08:08 -04'00'

Francisco Vicenty

Prepared: FVicenty: 08/11/2014

CTS No.: ICC1300542

NDA 205692

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/s/

STEVEN B HERTZ
08/12/2014

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

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

Memorandum

Date: August 7, 2014

To: Callie Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 205692 BASAGLAR (insulin glargine injection) for subcutaneous use

On October 22, 2013 OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Patient Information (PPI), Instructions for Use (IFU), and Carton and Container labeling for Basaglar. OPDP's comments on the proposed draft PI and Carton and Container labeling are based on the version available at <http://sharepoint.fda.gov/orgs/CDER-ODEII-DMEP/apps/NDA/N205692> on August 7, 2014.

OPDP's comments on the PI are provided directly on the marked version below. We have no comments on the Carton and Container labeling at this time.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the PPI and IFU under separate cover.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
08/07/2014

**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: July 29, 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)
Ankur Kalola, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)

Drug Name (established name): BASAGLAR (insulin glargine injection)

Dosage Form and Route: for subcutaneous use

Application Type/Number: NDA 205692

Applicant: Eli Lilly and Company

1 INTRODUCTION

On October 17, 2013, Eli Lilly and Company, submitted for the Agency's review a New Drug Application (NDA 205692) for BASAGLAR (insulin glargine injection) for subcutaneous use, a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

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 October 22, 2013 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for BASAGLAR (insulin glargine injection) for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed April 10, 2014.

2 MATERIAL REVIEWED

- Draft BASAGLAR (insulin glargine injection) PPI and IFU received on March 27, 2014, and received by DMPP on July 24, 2014.
- Draft BASAGLAR (insulin glargine injection) PPI and IFU received on March 27, 2014, and received by OPDP on July 24, 2014.
- Draft BASAGLAR (insulin glargine injection) Prescribing Information (PI) received on October 18, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on July 24, 2014.
- Draft BASAGLAR (insulin glargine injection) Prescribing Information (PI) received on October 18, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on July 24, 2014.

3 REVIEW METHODS

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 PPI document using the Verdana font, size 10.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The PPI and IFU 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 PPI and IFU 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 PPI and IFU.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
07/29/2014

ANKUR S KALOLA
07/29/2014

MELISSA I HULETT
07/29/2014

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

DATE: July 18, 2014

TO: Jean-Marc P. Guettier, M.D.
Director, Division of Metabolism and Endocrinology
Products

FROM: Michael F. Skelly, Ph.D., Pharmacologist
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

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

SUBJECT: Review of EIRs covering NDA 205-692, (b)(4) KwikPen
(Insulin Glargine injection), sponsored by Eli Lilly
and Company

At the request of the Division of Metabolism and Endocrinology Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence (I4L-MC-ABEO) and comparative bioavailability (I4L-MC-ABEN) studies:

Study Number: I4L-MC-ABEO
Study Title: "Comparative Pharmacokinetics and Pharmacodynamics of LY2963016 and US-Approved LANTUS® after Single-Dose Subcutaneous Administration to Healthy Subjects"

Study #: I4L-MC-ABEN
Study Title: "Bioequivalence of US LANTUS® to EU LANTUS® after Single-Dose Subcutaneous Administration to Healthy Subjects"

The inspection of the clinical portions of the studies was conducted by Anthony Keller (ORA Investigator, SAN-DO) at Lilly-NUS Centre for Clinical Pharmacology Pte. Ltd., at the National University of Singapore, in Singapore, from May 26 to May 30, 2014. There were no objectionable findings during the inspection and Form FDA-483 was not issued. Mr. Keller collected reserve samples of test and reference products used in study I4L-MC-ABEO, subject to 21 CFR 320.38(b)(3).

The inspection of the bioanalytical portions of the studies was conducted by (b)(4)

(b)(4)

The bioanalyses at (b)(4) were limited to measurement of total insulin (insulin glargine plus endogenous insulin). Assays for insulin C-peptide, to adjust for endogenous insulin reactivity in the total insulin assay, and the calculations for the adjustments, were conducted elsewhere, so they were not verified during the inspection. 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 studies I4L-MC-ABEN and I4L-MC-ABEO are acceptable for Agency review.

Michael F. Skelly, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

Lilly-NUS Centre for Clinical Pharmacology Pte. Ltd., National University of Singapore, Singapore - NAI
(FEI# 3004358483)

(b)(4) - NAI
(FEI# (b)(4))

Page 3 - NDA 205-692, (b) (4) KwikPen (Insulin Glargine injection), sponsored by Eli Lilly and Company

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Dejernet/CF

OSI/DBGLPC/BeB/Haidar/Choi/Skelly

OSI/DBGLPC/GLPB/Bonapace/Dasgupta

CDER/OND/ODEII/DMEP/Guettier/Cappel-Lynch

CDER/OND/OCP/Khurana/Lokesh Jain

ORA/SAN-DO/Keller

ORA/BLT-DO/Dan

Draft: MFS 7/18/2014

Edits: SHH 7/18/2014

OSI: File (b) (4); O:\BE\EIRCOVER\205692.Lil.InsGlarg.doc

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: (b) (4)

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/s/

MICHAEL F SKELLY
07/18/2014

SAM H HAIDAR
07/18/2014

WILLIAM H TAYLOR
07/22/2014



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: July 11, 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: Callie Cappel-Lynch, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 205692**
Applicant: Eli Lilly and Company
Drug Constituent: Insulin Glargine
Device Constituent: (b) (4) KwikPen
Intended Use: treatment of diabetes mellitus (types I and II)
CDRH CTS Tracking No.: 1300237

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Date: 2014.07.15 15:28:19 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ronald D. Kaye -S

Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Ronald D. Kaye -S,
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Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA 205692

Applicant: Eli Lilly and Company

Drug Constituent: Insulin Glargine

Device Constituent: (b) (4) KwikPen

Intended Use: treatment of diabetes mellitus (types I and II)

CDRH Human Factors Involvement History

- 10/22/2013: CDRH HFPMET was requested to review the human factors studies for the (b) (4) KwikPen to be used for delivery of insulin glargine
- 11/27/2013: CDRH HFPMET contacted the project manager regarding the location of the HF report within the submission for filling purposes.
- 12/2/2013: CDRH HFPMET was provided the report location (section 3.2.R.3.4.3, attachment 3 within the Global Submit)
- 6/27/2014: CDRH HFPMET indicated that there are no issues, and confirmed that DMEPA is in agreement.
- 7/16/2014: 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 report contained in the NDA submitted by Eli Lilly. The device constituent is the (b) (4) KwikPen platform for delivery of insulin glargine for treatment of diabetes mellitus.

On July 22, 2011, a Type C meeting was held with FDA where Lilly's intent was shared to use the KwikPen platform for multiple products in development. FDA agreed that the KwikPen platform is a viable pen design for the multiple Lilly products in development. FDA noted that KwikPen insulin products have been marketed for a number of years without significant user problems or product quality issues. Lilly was advised to systematically evaluate use-related risks related to multiple products in KwikPen and to develop a risk mitigation strategy for each product. The FDA did note potential drug confusion by healthcare providers or patients who would use more than one KwikPen product. Lilly has also identified this risk and has implemented mitigations to address this risk.

The study results identified 10 differentiation errors, which can be attributed to the subject not understanding the purpose of the task which can be linked directly to how the scenarios were communicated to the subjects. There were three errors in which subjects chose the pen based on what they are currently using. It was concluded that none of the observed errors with those that understood the task were due to label readability. No differentiation errors were identified that were attributable to the appearance of the (b) (4) KwikPen. In addition, there were 2 use errors where subjects dialing the 2-unit prime dose instead of the prescribed dose, 5 use errors where subjects did not complete the injection stroke and get the dial to return to zero, and 3 use errors

where subjects did not remove the inner needle shield before attempting to perform the injection. These errors could result in underdosing, which was determined to could have resulted in non-severe hyperglycemia. Eli Lilly claimed that none of the errors would have resulted in severe harm.

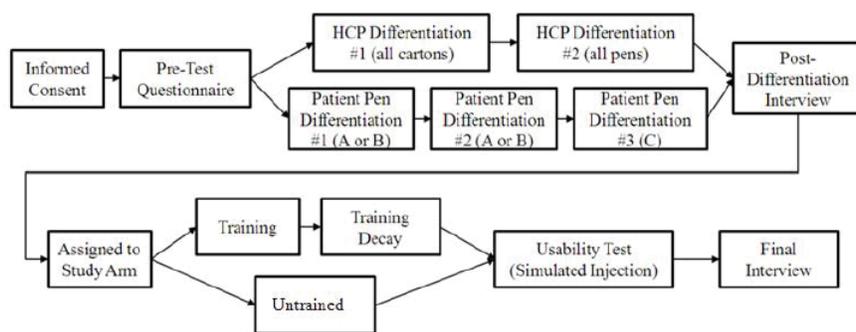
Recommendation:

Review of the human factors report found the study results to be acceptable. No further mitigations and/or modifications are necessary.

Appendix 1: Summary of Human Factors Validation (Summative) Study Design

A simulated use validation Human Factors test was conducted in January and February 2013 to validate the usability of the (b) (4) KwikPen device for use by 84 representative users. Intended users of (b) (4) KwikPen include patients, non-professional caregivers, and healthcare professionals. The device contains 300 units (total volume 3 mL) insulin (100 units/mL) and is capable of delivering from 1 to 60 units in a single injection. This device is intended for use anywhere users might administer insulin.

Lilly anticipates that nurses and diabetes educators will be trained in order to train patients and caregivers to use this device. Other (b) (4) KwikPen users are expected to receive training before using the device independently. Lilly also includes a telephone call center phone number in the IFU to help users who have difficulties using the device. In the study, the trained patients and caregivers were shown how to use the device, and performed a return demonstration of an injection. A training decay of at least one hour was observed to simulate the time between training and first use of the device. The study design is captured in the flow map below:



It is worth noting that Eli Lilly provides in Table 6.2 of the attachment a list of known pen injector problems, including those cited above, and the associated solutions that have been incorporated in the (b) (4) KwikPen as well as in the KwikPen platform. Using a risk management process that aligns with ISO 14971, Lilly also performed an analysis of the use-related risks via Application Failure Modes and Effects Analysis (AFMEA) to develop study methodology and identify and prioritize study tasks. The following table provides the evaluation of potential harm and associated severity.

Result of Use Error	Potential Harm	Severity
Under dose 5-100%	May result in non-severe hyperglycemia	Moderate
Overdose 5-50%	May result in non-severe hypoglycemia	Moderate
Overdose 50-100%	May result in severe hypoglycemia requiring the assistance of a third party	Major
Overdose >100% (absolute error >2 units)	May result in severe hypoglycemia requiring the assistance of a third party or may result in death	Severe

Appendix 2: Device Description

The (b) (4) KwikPen is a prefilled, disposable, mechanical pen injector containing 300 units of LY2963016, a long-acting (basal) insulin formulation. The (b) (4) KwikPen is a variation of the currently marketed KwikPen. Both pens share the internal dosing mechanism and principle of operation; and both comply with ISO11608-1. The (b) (4) KwikPen is intended for use with a standard disposable pen needle (supplied separately). The pen injector is intended to allow the user to dial and subcutaneously inject a dose ranging from 1 to 60 units (U) in single unit increments.

The (b) (4) KwikPen and the currently marketed KwikPen differ in the following ways:

- The Bezel on the outside of the pen body was modified to accommodate a 40% wider label.
- The Dose Knob has a printed color ring to match the color on the wider label and on the IFU.
- Cosmetic change to the side cutout of the Dose Knob.
- The shape of the Cap has been changed to give the device a more rounded appearance.
- The Dose Indicator is reshaped to enable the contrast color printing.
- The color of the pen is light gray compared with the currently marketed Humalog KwikPen (blue) and Humulin KwikPen (beige).



Figure 1 (b) (4) KwikPen

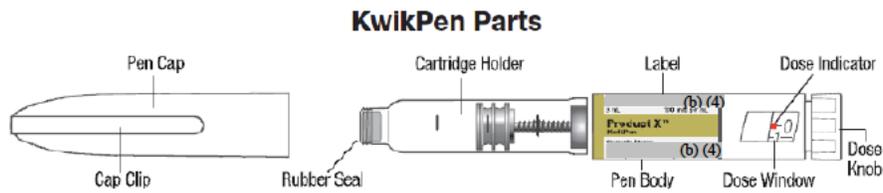


Figure 2 (b) (4) KwikPen Parts

Table 6-1 KwikPen Comparison

	Body Color	Button	Label Width	Cap	Pen Image
(b) (4)	Light Gray	Light Gray with Yellow Ring	35 mm	Rounded	
Humalog 600 Unit	Dark Gray	Dark Gray with Burgundy Ring	35mm	Rounded	
Humulin N	Beige	Green	25 mm	Square	
Humalog	Blue	Blue	25 mm	Square	

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/s/

CALLIE C CAPPEL-LYNCH
07/16/2014
signing for Quynh Nhu Nguyen



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

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1790

Memorandum

Date: 5/13/2014
Subject: Response to Information Request dated 08 April 2014.

Primary Reviewer: Faruk Sheikh, Ph.D., Laboratory of Immunology
Secondary Reviewer: Daniela Verthelyi, MD, Ph.D., Chief, Laboratory of Immunology

IND: NDA 205692 (Insulin Glargine, produced in *E.coli*)
Indication: Type 1 and Type 2 Diabetes Mellitus
Dose: LY2963016 (100U/mL) and LANTUS® (100U/mL); QD SC.

Sponsor: Eli Lilly

RPM: CappelLynch, Callie

10-Month User Fee Goal Date: August 18, 2014

Recommendation: Approval

There appeared to have no significant differences in immune response between LY2963016 and LANTUS® treatment for the patients (T1DM and T2DM) with respect to detectable antibodies and cross-reactivity at any visit. The immunogenicity profile was similar with LY2963016 and LANTUS®.

Background:

Eli Lilly submitted this NDA (insulin glargine) for LY2963016 (or Basalgar) under section 505(b)(2) of FDA act. Eli Lilly used FDA approved LANTUS® (Sanofi-Aventis) as the reference licensed product. The Sponsor included both US and EU approved LANTUS® in their study, but the immunogenicity results were not available separately for US and EU products. It appears that all insulin glargine products marketed by Sanofi-Aventis under the trade name LANTUS® are supplied from the same manufacturing site in (b)(4) and therefore it would be expected that there are no differences between US- and EU-approved LANTUS®. Eli Lilly conducted studies to compare US- and EU-approved LANTUS® to LY2963016 supporting this expectation (Refer to nonclinical, clinical and CMC review for details).

The primary amino acid sequence of LY2963016 is (b)(4) for LANTUS®, both are produced in *E.coli*. The safety profile and immunogenicity of LY2963016 in patients

with T1DM (study ABEB) and T2DM (study ABEC) was evaluated by the sponsor in two Phase 3 studies (n=1291). The patients were randomized into 2 groups (n= 648 for LY2963016; n= 647 for LANTUS®). The Sponsor stated that 60% of the T2DM patients enrolled in Study ABEC were insulin-naïve. The patients were randomized and the immunogenicity results for treatment naïve and switchover patients were not available separately (data on the breakdown of the ADA positive samples provided by the sponsor following an information request indicates no difference in the number of treatment naïve subjects that developed ADA) .

Upon review the submission, FDA requested additional information. In response to FDA information request dated 08 April, 2014, the Sponsor submitted additional data on 13 May, 2014 the review of which is included in this memo.

Dosing: LY2963016 is administered as a subcutaneous injection at 0.5U/kg dose for once-daily and is made available in a 3 mL cartridge sealed in a prefilled pen injector (KwikPen™).

ABEB (T1DM): 52-week study (24-week treatment period and 28-week extension period)

ABEC (T2DM): 24-week treatment study

Executive Summary:

The ABEB study (T1DM, 52 weeks), tested 536 patients (269:267). 17% (n=45/269) of the patients treated with LY2963016 were baseline positive for the presence of antibodies to insulin, compared to 20% (n=55/267) baseline positive patients treated with LANTUS®. The total number of patients with detectable antibodies to insulin LY2963016 and to LANTUS® were similar (n=113 of 269 and n=113 of 267) for an overall rate of 42%. In patients that received LY2963016, 73 of 113 ADA+ patients remained ADA positive at the end of the study (week 52), compared to 59 of 113 patients who were treated with LANTUS®. Binding antibody levels among those that were ADA+ at visit 11 (last visit) was low (<1% total binding by RIP) for 37(51%) and 31 (52%) patients respectively. The fraction of ADA+ samples that crossreacted with insulin was similar for both treatment groups (n=53 and 51 for LY2963016 and LANTUS® respectively).

The ABEC (T2DM, 24 weeks) studies tested immunogenicity in 744 T2DM patients. The total number of patients that were positive for ADA at least once during the study was 62 for LY2963016 and 49 for Lantus treated patients. At baseline, 20 subjects in the LY2963016 group were positive for ADA compared to 13 subjects that received Lantus; their antibody levels did not change significantly during the study. Seroconversion rate were similar between groups with 12.6% of LY2963016 and 10.7% Lantus- treated patients. At the end of the study (24 weeks), 30 patients remained positive for LY2963016, compared with 26 positives for Lantus.

The Sponsor assessed the impact of antibody formation on safety and efficacy using assays that measure HbA1c, basal insulin dose, and rate of total Hypoglycemia and concluded that there were no statistically significant treatment differences observed for the patients with detectable antibodies (quantified as percent binding) at baseline, endpoint, or overall.

We conclude that there were no statistically or clinically significant differences observed in these studies that would indicate a difference in immunogenicity risk.

T1DM (ABEB)	BASALGAR	LANTUS
Total Study population, n=	269	267
ADA Positive		
ADA+ at least at one point	113	113
Baseline ADA+ positive	46	55
Baseline ADA+ did not change titer	29	33
Seroconvert ADA+	113-29 = 84 (31%)	113-33 = 80 (30%)
ADA Positive		
ADA Positive		
T2DM (ABEC)	BASALGAR	LANTUS
Total (including treatment naive), n=	379	365
ADA Positive		
ADA+ at least at one point	62	49
Baseline ADA+ positive	20	13
Baseline ADA+ did not change titer	14	10
Seroconvert ADA+	62-14 = 48 (12.6%)	49-10 = 39 (10.7%)
No previous treatment at entry	32	36
Switched from Lantus	30	13

On 08 April, 2014 the FDA requested for the following information (Immunogenicity):

FDA Q1: Your data indicated that the number of patients with detectable insulin antibodies at week 52 in study ABEB was similar to LANTUS® (LY2963016: 40.4% to LANTUS®: 39.3%). However, in the 24 week ABEC study, at least 4% more subjects had (b) (4) antibodies than those treated with LANTUS® (Table ABEC 12.14). There is concern regarding the clinical impact of these antibodies. To help elucidate this question please provide the following information:

1. Samples that are positive for the presence of anti-drug antibody at least one time point during the course of the study, should be considered to be an anti-drug antibody (ADA) positive sample, regardless of the patient's ADA status at baseline. Confirm that overall number of ADA+ patient from both treatment group included patients who were ADA+ for at least one time-point of the study.

Lilly Response to Q1.1: We can confirm that the proportion of patients with detected antibodies during Studies ABEB and ABEC included any patient who had the presence of antidrug antibody (% binding ≥ 0.26) for at least 1 time point during the course of the study independent of baseline status.

Reviewer's comment: *The Sponsor confirmed that any patient who had the presence of antidrug antibody (% binding ≥ 0.26) for at least 1 time point during the course of the study independent of baseline status was reported as antibody positive. The Sponsor provided a supportive data listings that are presented in Tables APP.14 (Appendix1). The data illustrated that 113 of 279 patients treated with LY2963016 and 113 of 267 treated with LANTUS® were ADA+ in ABEB studies (T1DM, 52 weeks), whereas in ABEC (T2DM, 24 weeks) studies, overall number of patients with detectable antibodies to insulin LY2963016 were 15.8% (n=60/379) at visit 16 (24 weeks) of the treatment, compared to 13.1% patients (n=48/365) treated with LANTUS®. The data indicated that more number of patients from T1DM is ADA+ than patients from T2DM. Overall, the immunogenicity profile with insulin LY2963016 and LANTUS® is similar.*

2. You are using antibodies raised against LY2963016 in your assays as reference standards. Provide data demonstrating that these antibodies bind with equal affinity to Lantus and LY2963016.

Lilly Response to Q1.2: The affinity-purified polyclonal antibody used as a positive control in the assay was derived from guinea pigs that were hyperimmunized with regular insulin, not LY2963016 or LANTUS®. Therefore, the positive control should not be biased with regard to detection of LY2963016 versus LANTUS®.

Reviewer's Comment: *The primary amino acid sequence of LY2963016 and LANTUS® ^{(b) (4)} this sequence differs from native insulin by one amino acid in A-chain and by two C-terminal amino acid of B-chain. Therefore it is expected that the antibodies would bind with similar efficiency to detect LY2963016 and LANTUS®.*

3. Provide the titer of the antibodies induced in ADA positive samples.

Lilly Response to Q1.3: For the Phase 3 studies, antibody measurements were quantified as percent binding. After adding a radiolabeled tracer (LY2963016) to a serum sample, percent binding represents the percent of the total amount of tracer that co-precipitated with the antibodies. Similar to titers, it is a method of quantifying the amount of antibody in a sample. Unlike titers, it is a continuous variable. This technique has been previously used in LANTUS® registration studies (Ratner et al. 2000; Home et al. 2005). For Studies ABEB and ABEC, individual patient listings showing percent binding levels at all visits, sorted by treatment and maximum % binding level (Table APP. 14 and APP. 15), are provided in the [Appendices](#).

Reviewer's Comment: *The Sponsor did not assess titer instead they measured the amount of insulin antibody in a sample quantitatively using a radioactive tracer. The results are expressed as percent binding level which is claimed to be similar to titer. In ABEB studies, 52 of 113 ADA+ patients (46%) treated with LY2963016 had amount of antibodies greater than 1, compared to 51 of 113 patients (45%) treated with LANTUS®. On the other hand, 18 of 60 ADA+ patients (30%) treated with LY2963016 had levels of antibodies greater than 1, compared to 19 of 48 patients (39%) treated with LANTUS® in ABEC studies.*

FDA Q2.1: Provide data on the cross-reactivity of the antibodies to LY2963016 with native insulin.

Lilly Response to Question 7: Cross-Reactivity of Antibodies

It is important to note that in the original submission analyses of insulin antibody levels (% binding) were conducted only in patients who had a detected antibody formed against LY2963016, both at baseline and at least 1 post baseline visit. In this regulatory response, analyses of % binding include any patient in the FAS who had a detected antibody at any point during the study, representing a larger sample than that included in the original submission. Further, analyses of cross-reactive antibodies were conducted to confirm that the immune response of LY2963016 and LANTUS® are similar with respect to antibodies formed against native insulin. This regulatory response presents plots of detected total and cross-reactive insulin antibody levels. Additionally, the datasets for cross-reactive antibodies to native insulin have been submitted with this response. Study ABEB: For the roughly 40% of the FAS population with detected antibodies at any point during the 52-week treatment period, insulin antibody levels (total and cross-reactive) as measured by % binding were low and similar between treatment groups. There were no significant differences in median % binding between LY2963016 and LANTUS® at any visit or endpoint for total or cross-reactive insulin antibody levels in the FAS (Figure 4.4 and Figure 4.5). The levels of cross-reactive insulin antibodies over time followed a similar pattern to that of total insulin antibodies in both the LY2963016 and LANTUS® treatment groups. Full summaries of descriptive statistics for total and cross-reactive antibody levels in the FAS population are in Appendix 2. Study ABEC: Of the approximately 13% of the FAS population with detected antibodies at any point during the 24-week treatment period, insulin antibody levels (total and cross-reactive) as measured by % binding were similar between treatment groups. There were no significant differences in median % binding between LY2963016 and LANTUS® at any visit or endpoint for total or cross-reactive insulin antibody levels in the FAS (Figure 4.6 and Figure 4.7). The levels of cross-reactive insulin antibodies over time followed a similar pattern to that of total insulin antibodies in both the LY2963016 and LANTUS® treatment groups. Full summaries of descriptive statistics for total and cross-reactive antibody levels in the FAS population are in Appendix 2.

Study ABEB:

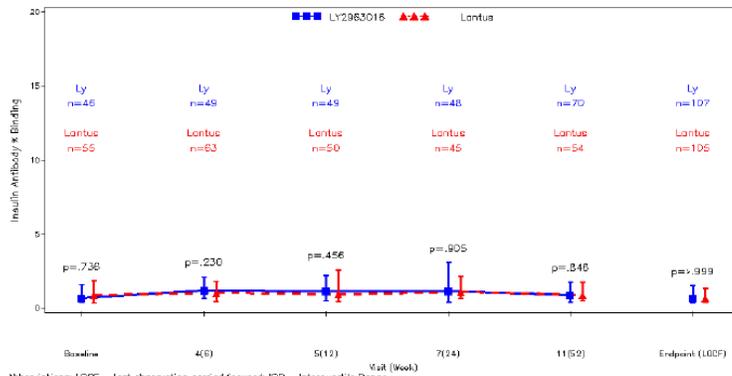


Figure 4.5. Total insulin antibody levels (% binding) by treatment, visit, and endpoint –Study ABEB: full analysis set.

Note: In this figure, the levels of insulin antibodies generated by LY2963016 and LANTUS® treatment with visit are compared using % binding. There appeared to have no significant differences in % binding between LY2963016 and LANTUS® at any visit or endpoint for total insulin antibody levels in the full analysis sets (FAS).

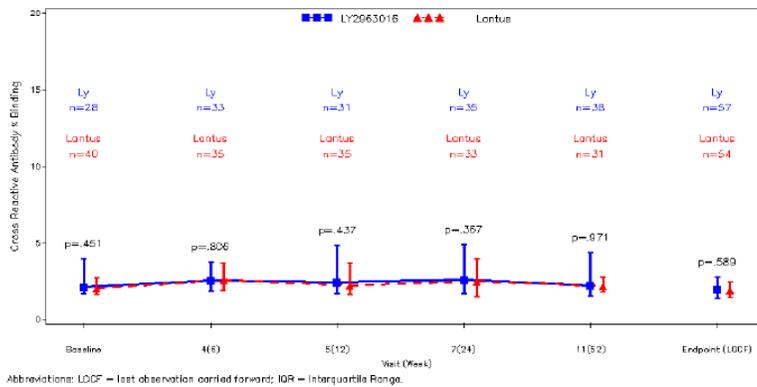


Figure 4.6. Cross-reactive insulin antibody levels (% binding) by treatment, visit, and endpoint –Study ABEB: full analysis set.

Note: In this figure, the levels of % binding of cross-reactive insulin antibodies are compared with visit. There appeared to have no significant differences between LY2963016 and LANTUS® at any visit or endpoint.

Study ABEC:

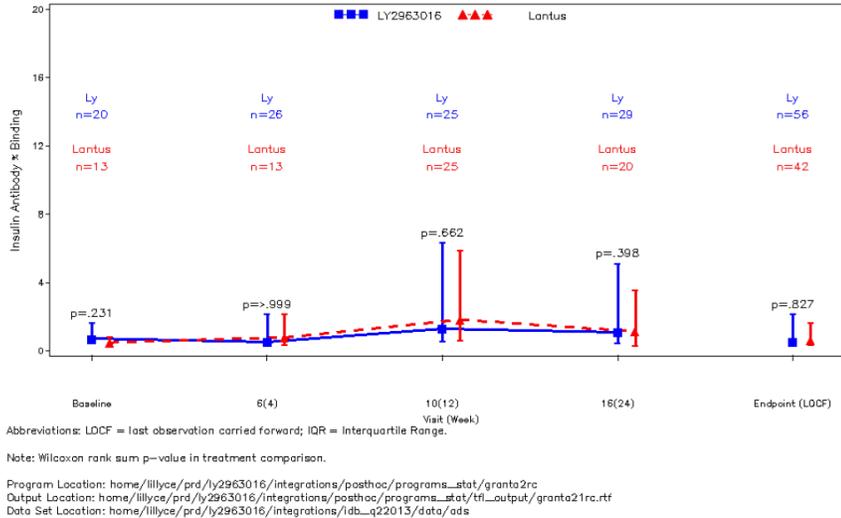


Figure 4.7. Total insulin antibody levels (% binding) by treatment, visit, and endpoint –Study ABEC: full analysis set.

Note: The levels of insulin antibodies % binding are compared between LY2963016 and LANTUS® treatment groups with visit. Although the error bar is wider at visit 12 and visit 24 for both treatment groups, the figure showed that insulin antibody levels as measured by % binding were similar between treatment groups. There were no significant differences in % binding between LY2963016 and LANTUS® at any visit or endpoint for total insulin antibody levels.

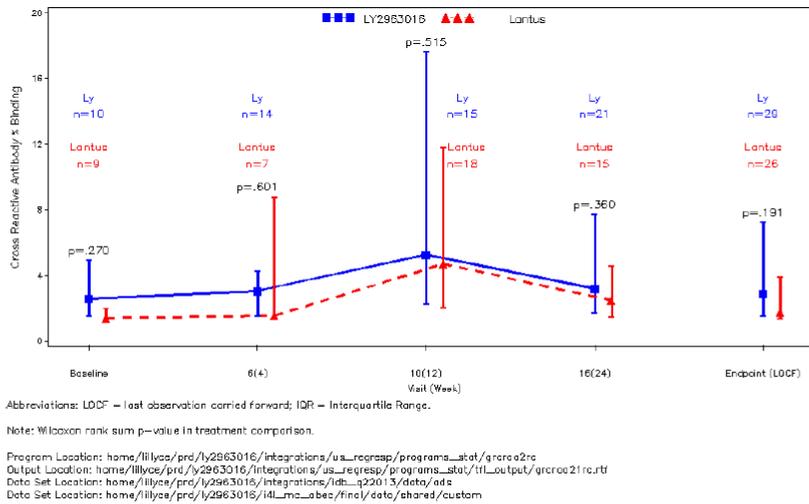


Figure 4.8. Cross-reactive insulin antibody levels (% binding) by treatment, visit, and endpoint–Study ABEC: full analysis set.

Note: The levels of cross-reactive insulin antibodies % binding are compared between LY2963016 and LANTUS® treatment groups with visit. Although the error bar is wider for both treatment groups, the figure showed that cross-reactive insulin antibody levels as measured by % binding were similar between treatment groups. There were no significant differences in % binding between LY2963016 and LANTUS® at any visit or endpoint for total cross-reactive insulin antibody levels.

Reviewer's Comment: *The ADA+ samples from both treatment group in ABEB studies, were assessed for cross-reactivity which were similar (n=52 and 51 for LY2963016 and LANTUS® respectively). At the end (visit16) of ABEC studies, also had similar cross-reactivity profile for both treated group of patients (n=27 and 29 for LY2963016 and LANTUS® respectively). Therefore, the levels of cross-reactive insulin antibodies were similar between groups of LY2963016 and LANTUS® treatment.*

FDA Q2.2: Additionally, if you have data on the neutralizing capacity of these antibodies, please provide it for review.

4.2.4. Lilly Response to Question 7: Neutralization Capacity of Antibodies

While we do not have neutralizing immunogenicity data, in order to evaluate for the possibility of neutralization capacity of antibodies clinically, Lilly has assessed key clinical parameters (HbA1c, insulin dose, and hypoglycemia) in relation to antibody status and has found no evidence of neutralization of glucose-lowering effect by insulin antibodies. This data was provided in the original submission (refer to Module 2.7.4.3.2.2).

Reviewer's Comment: *The Sponsor does not have neutralizing immunogenicity data. In absence of neutralizing antibody assay, the clinical parameters can be assessed for the possibility of the neutralizing capabilities of anti-insulin antibodies, which is a part of clinical review. Nevertheless, this is a 505(b) application and the Sponsor sufficiently evaluated to show that insulin LY2963016 and LANTUS® are similar with respect to their immunogenicity profile.*

Appendix1:

The following table shows visit-wise antibody status of ADA+ patients' from Phase3 study ABEB. The patients were treated with LY2963016.

Table APP.14. Insulin Antibodies Sorted by Treatment and Maximum Postbaseline % Binding Full Analysis Set: Patients with Detectable Antibodies at Any Visit Study I4L-MC-ABEB: Overall Study (Treatment and Extension)

Inv	Pat	Treatment	Entry Insulin	Visit 2 Week 0	Visit 4 Week 6	Visit 5 Week 12	Visit 7 Week 24	Visit 11 Week 52
20	2009	LY2963016	Lantus	17.63NT	19.77CR	19.84CR	22.90CR	30.41*CR
50	5025	LY2963016	Other	ND	ND	0.84*CR	13.16*CR	1.51*CR
62	6205	LY2963016	Other	ND	8.36*CR	12.19*CR	6.84*CR	DO
69	6914	LY2963016	Other	13.82CR	10.53CR	9.53CR	6.33CR	3.24CR
62	6206	LY2963016	Lantus	10.37CR	8.05CR	8.78CR	5.66CR	7.96CR
54	5403	LY2963016	Other	ND	ND	7.51*CR	3.44*CR	0.89*CR
29	2901	LY2963016	Lantus	ND	ND	ND	7.45*CR	5.03*CR
50	5007	LY2963016	Lantus	1.59CR	2.57CR	2.65*CR	2.97*CR	7.30*CR
68	6801	LY2963016	Lantus	1.55CR	1.53CR	1.60CR	3.11*CR	6.17*CR
8	804	LY2963016	Lantus	3.98CR	4.23CR	4.03CR	6.06*CR	4.39CR
13	1307	LY2963016	Other	3.76CR	3.57CR	5.29*CR	4.99*CR	4.54CR
10	1003	LY2963016	Lantus	1.35CR	4.91*CR	3.90*CR	1.70CR	5.17*CR
40	4000	LY2963016	Lantus	ND	ND	1.13*CR	2.26*CR	5.15*CR
42	4202	LY2963016	Other	3.44CR	4.18CR	3.71CR	3.73CR	1.73CR
49	4916	LY2963016	Lantus	0.68NCR	2.00*NCR	1.13NCR	3.82*CR	2.95*NCR
53	5305	LY2963016	Lantus	ND	ND	ND	ND	3.66*CR
76	7600	LY2963016	Lantus	0.46CR	3.15*CR	1.85*CR	ND	1.71*CR
18	1801	LY2963016	Lantus	1.35CR	1.43CR	1.55CR	3.06*CR	DO
98	9802	LY2963016	Lantus	1.00CR	1.66CR	2.58*CR	3.06*CR	1.07CR
98	9813	LY2963016	Lantus	0.30CR	0.65CR	2.99*CR	2.64*CR	1.76*CR
49	4904	LY2963016	Lantus	1.68CR	2.77*CR	2.23CR	2.16CR	1.65CR
19	1905	LY2963016	Lantus	ND	0.95*CR	1.00*CR	0.56*CR	2.58*CR
12	1201	LY2963016	Lantus	1.77CR	2.05CR	2.08CR	1.48CR	2.55CR
50	5010	LY2963016	Lantus	0.37NCR	ND	2.16*NCR	ND	2.41*CR
31	3100	LY2963016	Lantus	2.59CR	1.77CR	1.10NCR	1.20NT	2.22NT
12	1208	LY2963016	Lantus	2.01CR	2.21CR	0.33CR	0.39CR	1.69NCR
63	6306	LY2963016	Lantus	0.59NCR	2.11*CR	2.13*CR	ND	ND
1	103	LY2963016	Lantus	0.27CR	1.96*CR	ND	1.13CR	1.36*CR
9	909	LY2963016	Lantus	ND	ND	NT	ND	1.85*CR
21	2108	LY2963016	Other	ND	0.49*CR	ND	1.77*CR	1.53*CR
43	4303	LY2963016	Other	ND	0.92*CR	0.95*NCR	1.67*CR	0.92*CR
44	4404	LY2963016	Lantus	0.91NCR	1.65CR	ND	ND	ND
69	6907	LY2963016	Lantus	ND	ND	1.56*CR	ND	0.66*NCR
10	1004	LY2963016	Other	ND	ND	1.46*NCR	ND	ND
69	6908	LY2963016	Other	2.19CR	1.44CR	0.55CR	1.27CR	1.07NCR
50	5006	LY2963016	Other	ND	ND	1.43*NCR	0.31*NCR	ND
3	300	LY2963016	Lantus	0.62CR	1.42CR	DO	DO	DO
78	7804	LY2963016	Lantus	ND	1.34*CR	0.38*CR	0.81*CR	1.14*CR
8	800	LY2963016	Lantus	ND	ND	ND	0.81*CR	1.24*CR
8	820	LY2963016	Lantus	ND	ND	0.30*NCR	0.36*CR	1.24*CR
44	4405	LY2963016	Lantus	ND	ND	1.24*NCR	ND	0.47*NCR
63	6303	LY2963016	Lantus	ND	1.20*NT	ND	ND	DO
16	1601	LY2963016	Lantus	0.56CR	1.19CR	1.02CR	0.27CR	0.27CR
51	5101	LY2963016	Lantus	0.85CR	1.19NCR	0.54CR	ND	ND
49	4918	LY2963016	Lantus	ND	ND	ND	ND	1.14*CR
67	6704	LY2963016	Other	1.25CR	1.08CR	ND	ND	0.57CR
11	1103	LY2963016	Other	0.52CR	ND	ND	ND	1.06NCR
97	9713	LY2963016	Lantus	ND	ND	1.02*CR	0.83*CR	0.79*NCR
9	907	LY2963016	Other	ND	1.00*CR	0.86*NCR	ND	ND
49	4913	LY2963016	Lantus	ND	ND	ND	ND	0.96*NCR
62	6207	LY2963016	Lantus	ND	0.93*NCR	ND	ND	ND
8	813	LY2963016	Lantus	0.46NCR	ND	0.38NCR	ND	0.90CR
11	1100	LY2963016	Lantus	0.66CR	0.34CR	0.84CR	0.31CR	ND
64	6400	LY2963016	Lantus	ND	0.84*NCR	ND	ND	0.51*NCR
61	6103	LY2963016	Other	0.33NCR	0.83NCR	ND	ND	ND
76	7609	LY2963016	Lantus	0.62NCR	0.76NCR	ND	ND	ND
20	2003	LY2963016	Lantus	0.36NCR	ND	ND	0.74NCR	ND
67	6700	LY2963016	Lantus	ND	ND	0.74*NCR	ND	0.34*NCR
97	9705	LY2963016	Lantus	ND	ND	ND	ND	0.72*CR
6	607	LY2963016	Lantus	ND	ND	ND	ND	0.70*NCR
13	1303	LY2963016	Lantus	ND	ND	ND	ND	0.70*NCR
44	4412	LY2963016	Lantus	ND	ND	ND	ND	0.70*CR
51	5109	LY2963016	Other	ND	ND	ND	ND	0.70*NCR
8	814	LY2963016	Lantus	ND	ND	ND	ND	0.69*NCR
98	9810	LY2963016	Lantus	ND	0.66*NCR	0.32*CR	ND	ND
9	903	LY2963016	Lantus	ND	ND	ND	ND	0.63*CR
69	6901	LY2963016	Other	0.29NCR	ND	ND	0.60NCR	ND
31	3109	LY2963016	Lantus	1.01CR	0.51CR	0.33CR	ND	0.58CR
43	4300	LY2963016	Other	ND	0.57*CR	ND	ND	ND
50	5012	LY2963016	Lantus	0.28NCR	ND	ND	0.57NCR	0.33CR
49	4912	LY2963016	Lantus	0.53NCR	0.56NCR	ND	ND	ND
17	1708	LY2963016	Lantus	ND	ND	ND	0.55*NCR	0.41*NCR
11	1108	LY2963016	Lantus	ND	ND	ND	0.54*CR	ND
45	4503	LY2963016	Lantus	ND	ND	ND	ND	0.53*NCR
49	4915	LY2963016	Lantus	1.07NCR	ND	0.53NCR	0.26NCR	ND

97	9715	LY2963016	Lantus	ND	ND	0.53*NCR	NT	ND
68	6808	LY2963016	Lantus	ND	ND	0.52*NCR	ND	ND
97	9710	LY2963016	Other	ND	ND	0.50*NT	ND	ND
29	2906	LY2963016	Lantus	ND	ND	ND	0.48*NCR	ND
2	200	LY2963016	Lantus	0.41CR	ND	ND	ND	0.47NCR
12	1203	LY2963016	Other	ND	0.46*NCR	ND	ND	ND
80	8003	LY2963016	Lantus	ND	ND	ND	ND	0.46*NCR
68	6806	LY2963016	Lantus	ND	ND	0.44*NCR	ND	ND
20	2005	LY2963016	Lantus	0.33NCR	ND	ND	ND	0.43NCR
80	8004	LY2963016	Other	ND	0.43*NCR	ND	ND	0.28*NCR
8	818	LY2963016	Lantus	ND	0.42*NCR	ND	0.36*NCR	ND
98	9805	LY2963016	Lantus	ND	0.41*NCR	ND	0.39*NCR	ND
74	7400	LY2963016	Lantus	ND	ND	ND	0.40*NCR	0.40*NCR
33	3303	LY2963016	Lantus	ND	0.39*NCR	ND	ND	ND
69	6904	LY2963016	Other	ND	ND	ND	0.37*NCR	ND
15	1503	LY2963016	Lantus	ND	ND	ND	0.36*CR	ND
67	6701	LY2963016	Lantus	ND	0.36*NCR	ND	ND	ND
30	3006	LY2963016	Lantus	ND	ND	ND	ND	0.34*NCR
31	3120	LY2963016	Lantus	ND	ND	ND	ND	0.32*NCR
37	3708	LY2963016	Lantus	ND	ND	ND	ND	0.32*NCR
19	1902	LY2963016	Lantus	ND	ND	ND	ND	0.31*NCR
31	3114	LY2963016	Lantus	ND	0.29*NCR	0.31*NCR	ND	ND
36	3600	LY2963016	Lantus	ND	ND	0.31*NCR	ND	ND
62	6202	LY2963016	Other	ND	ND	ND	ND	0.31*NCR
8	803	LY2963016	Lantus	ND	ND	ND	0.30*NT	ND
8	829	LY2963016	Lantus	ND	ND	ND	ND	0.29*NCR
50	5008	LY2963016	Lantus	ND	ND	ND	ND	0.29*CR
6	613	LY2963016	Lantus	ND	ND	ND	ND	0.28*NCR
49	4921	LY2963016	Lantus	ND	ND	ND	ND	0.28*NCR
33	3302	LY2963016	Other	ND	ND	ND	ND	0.27*NCR
6	609	LY2963016	Other	ND	ND	ND	0.26*CR	ND
33	3313	LY2963016	Lantus	ND	ND	ND	ND	0.26*NCR
4	400	LY2963016	Other	0.30NCR	ND	ND	ND	ND
12	1209	LY2963016	Other	1.53CR	DO	DO	DO	DO
19	1911	LY2963016	Lantus	0.67NCR	ND	ND	ND	ND
43	4301	LY2963016	Lantus	0.27NCR	ND	ND	ND	ND
68	6809	LY2963016	Lantus	0.69CR	ND	ND	ND	ND
80	8001	LY2963016	Lantus	0.32NCR	ND	ND	ND	ND

The following table shows visit-wise antibody status of ADA+ patients' from Phase3 study ABEB. The patients were treated with LANTUS®.

Listing of Insulin Antibodies Sorted by Treatment and Maximum Post Baseline % Binding
Full Analysis Set With Detectable Antibodies at Any Visit
Study I4L-MC-ABEB: Overall Study (Treatment and Extension)

Inv	Pat	Treatment	Entry Insulin	Visit 2 Week 0	Visit 4 Week 6	Visit 5 Week 12	Visit 7 Week 24	Visit 11 Week 52
12	1207	Lantus	Lantus	14.13CR	14.64CR	14.53CR	20.20*CR	17.61CR
10	1005	Lantus	Lantus	9.74CR	9.51CR	17.18*CR	15.60*CR	17.13*CR
98	9804	Lantus	Lantus	13.26CR	15.56CR	DO	DO	DO
9	904	Lantus	Lantus	6.90CR	12.68*CR	7.48CR	3.03CR	5.25CR
68	6807	Lantus	Lantus	ND	3.21*CR	5.98*CR	4.42*CR	0.89*NCR
9	911	Lantus	Lantus	4.85CR	4.14CR	4.09CR	4.89CR	4.34CR
56	5603	Lantus	Other	ND	2.59*CR	4.84*CR	4.47*CR	2.05*CR
18	1809	Lantus	Lantus	4.93CR	3.88CR	3.82CR	3.01CR	1.75CR
43	4302	Lantus	Other	3.91CR	2.99CR	3.51CR	1.67CR	2.10CR
98	9807	Lantus	Lantus	1.22CR	2.16CR	3.35*CR	3.48*CR	1.40CR
100	1065	Lantus	Lantus	2.78CR	2.45CR	3.42CR	2.62CR	1.75CR
8	809	Lantus	Lantus	ND	ND	0.46*CR	3.03*CR	2.07*CR

15	1500	Lantus	Lantus	1.84CR	1.71CR	0.93CR	0.34CR	3.02*CR
51	5106	Lantus	Lantus	2.54CR		2.67CR	2.82CR	2.80CR
63	6302	Lantus	Lantus	0.69CR	2.82*CR	2.68*CR	1.18CR	0.54NCR
100	1062	Lantus	Lantus	1.43CR	2.04CR	2.58*CR	1.77CR	0.79CR
69	6903	Lantus	Other	ND	0.62*NCR	ND	0.35*CR	2.43*CR
2	204	Lantus	Lantus	3.30CR	2.36CR	1.39NCR	ND	ND
36	3601	Lantus	Lantus	ND	NT	ND	0.61*CR	2.33*CR
6	605	Lantus	Other	3.04CR	2.18CR	1.24CR	ND	ND
74	7405	Lantus	Lantus	1.26CR	0.77CR	1.69CR	2.18CR	0.81CR
20	2008	Lantus	Lantus	ND	ND	ND	0.84*CR	1.84*NCR
54	5401	Lantus	Lantus	1.52CR	1.82CR	0.35CR	1.26CR	1.04CR
19	1910	Lantus	Lantus	ND	ND	ND	1.79*CR	1.06*CR
69	6913	Lantus	Other	ND	1.76*NCR	ND	ND	ND
76	7602	Lantus	Lantus	1.09CR	1.75CR	1.73CR	1.08CR	0.50CR
8	808	Lantus	Lantus	1.15CR	1.12CR	1.66CR	DO	DO
49	4907	Lantus	Lantus	1.27NCR	1.66CR	1.38CR	0.90CR	1.36CR
17	1707	Lantus	Lantus	3.37CR	1.64CR	1.45CR	ND	0.76CR
44	4401	Lantus	Lantus	0.31CR	1.42*CR	0.56NCR	1.10CR	1.63*CR
31	3112	Lantus	Lantus	ND	0.95*CR	1.14*CR	1.60*NCR	ND
29	2905	Lantus	Lantus	1.71CR	1.56CR	1.37CR	1.51CR	1.48CR
74	7402	Lantus	Lantus	0.41CR	ND	0.37CR	1.13CR	1.56*CR
22	2203	Lantus	Other	ND	ND	ND	ND	1.51*CR
45	4500	Lantus	Lantus	ND	ND	ND	ND	1.43*NCR
49	4925	Lantus	Lantus	0.93CR	1.14CR	1.43CR	ND	1.11CR
30	3000	Lantus	Lantus	0.30NCR	ND	0.38NCR	1.42*NCR	0.30CR
44	4406	Lantus	Lantus	0.35CR	1.42*NCR	ND	0.71NCR	ND
8	821	Lantus	Lantus	2.08CR	1.41CR	ND	ND	ND
78	7805	Lantus	Lantus	ND	ND	ND	ND	1.35*CR
64	6407	Lantus	Lantus	ND	ND	ND	1.34*NCR	0.98*NCR
69	6906	Lantus	Lantus	ND	1.26*CR	1.20*CR	ND	ND
63	6307	Lantus	Lantus	ND	1.20*NCR	0.61*NCR	ND	ND
8	826	Lantus	Lantus	ND	1.13*NCR	ND	ND	0.46*NCR
46	4603	Lantus	Lantus	1.13CR	1.13CR	0.65CR	0.32CR	ND
98	9806	Lantus	Lantus	0.51CR	1.04CR	0.67CR	1.09CR	0.29NCR
13	1302	Lantus	Lantus	0.26CR	1.05CR	0.51CR	DO	DO
52	5201	Lantus	Lantus	0.75CR	0.28CR	0.47CR	1.04CR	ND
97	9714	Lantus	Lantus	ND	ND	ND	1.02*NCR	ND
44	4407	Lantus	Lantus	0.77CR	ND	0.36NCR	0.99NCR	0.83NCR
64	6404	Lantus	Lantus	ND	0.96*NCR	ND	ND	ND
74	7406	Lantus	Lantus	ND	ND	0.94*NCR	ND	ND
64	6405	Lantus	Lantus	ND	ND	ND	0.90*NCR	ND
9	902	Lantus	Lantus	ND	ND	ND	ND	0.89*NCR
50	5015	Lantus	Lantus	ND	ND	ND	0.84*NCR	ND
97	9711	Lantus	Lantus	0.32CR	0.84CR	ND	ND	0.72CR
17	1706	Lantus	Lantus	1.58NCR	0.76NCR	ND	ND	ND
37	3709	Lantus	Lantus	ND	0.73*NCR	DO	DO	DO
31	3116	Lantus	Other	ND	ND	0.71*NCR	ND	ND
9	910	Lantus	Lantus	0.29CR	0.66NCR	0.70CR	ND	ND
56	5605	Lantus	Lantus	ND	ND	ND	ND	0.70*NCR
98	9812	Lantus	Lantus	ND	ND	ND	0.70*CR	ND
2	201	Lantus	Lantus	0.81CR	0.68CR	DO	DO	DO
50	5024	Lantus	Lantus	ND	ND	0.67*NCR	ND	ND
44	4413	Lantus	Lantus	ND	ND	ND	ND	0.66*CR
80	8000	Lantus	Other	0.70CR	0.37NCR	ND	0.65NCR	0.65NCR
49	4903	Lantus	Lantus	ND	ND	0.58*CR	ND	ND
10	1000	Lantus	Lantus	0.30NCR	0.56CR	ND	ND	ND
68	6805	Lantus	Lantus	ND	0.56*NCR	ND	ND	ND
8	825	Lantus	Lantus	ND	ND	ND	ND	0.55*NCR
8	827	Lantus	Other	ND	0.26*NCR	ND	ND	0.54*NCR
20	2010	Lantus	Lantus	ND	ND	ND	ND	0.54*CR
69	6905	Lantus	Lantus	ND	ND	ND	ND	0.54*NCR
8	823	Lantus	Lantus	ND	ND	ND	ND	0.50*NCR
14	1402	Lantus	Lantus	ND	0.50*NCR	ND	ND	ND
31	3119	Lantus	Lantus	0.88NCR	0.50NCR	ND	ND	ND
44	4402	Lantus	Lantus	ND	ND	ND	0.50*NCR	ND
51	5114	Lantus	Lantus	0.59NCR	ND	0.50CR	0.32CR	ND
70	7004	Lantus	Lantus	0.39NCR	0.50NCR	ND	0.44CR	ND
70	7005	Lantus	Lantus	ND	0.49*NT	ND	ND	ND
49	4914	Lantus	Lantus	ND	ND	ND	0.48*CR	ND
34	3407	Lantus	Lantus	ND	ND	ND	ND	0.47*NCR
8	817	Lantus	Lantus	0.38NCR	ND	0.45NCR	ND	0.31NCR
51	5113	Lantus	Lantus	ND	ND	ND	ND	0.44*NCR
63	6308	Lantus	Lantus	1.30NCR	0.44NCR	0.31NCR	ND	ND
54	5402	Lantus	Lantus	ND	0.43*NCR	ND	ND	ND
67	6702	Lantus	Lantus	ND	0.42*NCR	ND	ND	ND

13	1309	Lantus	Lantus	ND	0.41*NCR	ND	ND	0.27*NCR
50	5001	Lantus	Lantus	ND	0.41*NCR	ND	ND	ND
62	6204	Lantus	Other	0.55CR	ND	0.40NCR	ND	ND
13	1301	Lantus	Lantus	ND	ND	0.39*CR	ND	ND
51	5108	Lantus	Lantus	ND	0.39*NCR	ND	ND	ND
50	5005	Lantus	Lantus	ND	ND	0.38*NCR	ND	ND
100	1061	Lantus	Other	0.46NCR	ND	0.37NCR	ND	ND
41	4100	Lantus	Lantus	ND	ND	ND	ND	0.36*NCR
50	5023	Lantus	Lantus	0.28NCR	ND	ND	0.36NCR	ND
78	7806	Lantus	Lantus	ND	0.36*NCR	0.29*NCR	NT	ND
62	6210	Lantus	Other	ND	0.35*NCR	ND	ND	ND
68	6810	Lantus	Lantus	ND	0.35*NCR	ND	ND	ND
76	7605	Lantus	Other	ND	0.35*NCR	0.26*NCR	ND	ND
8	806	Lantus	Lantus	ND	ND	ND	ND	0.32*NCR
98	9801	Lantus	Lantus	ND	0.31*NCR	ND	ND	ND
6	611	Lantus	Lantus	ND	0.26*NCR	ND	ND	0.28*NCR
50	5003	Lantus	Lantus	ND	ND	ND	0.27*NCR	ND
67	6703	Lantus	Lantus	ND	ND	ND	ND	0.27*NCR
11	1101	Lantus	Lantus	0.49CR	ND	ND	ND	ND
31	3110	Lantus	Other	0.63CR	ND	ND	ND	ND
31	3123	Lantus	Lantus	1.13CR	ND	ND	ND	ND
37	3706	Lantus	Lantus	0.28NCR	ND	ND	ND	ND
39	3900	Lantus	Lantus	0.33CR	ND	ND	ND	DO
42	4201	Lantus	Lantus	0.27NCR	ND	ND	ND	ND
50	5018	Lantus	Lantus	0.44NCR	ND	ND	ND	ND
64	6401	Lantus	Lantus	0.36NCR	ND	ND	ND	ND

Abbreviations:

Inv = Investigator; Pat = Patient ID; TEAR = Treatment Emergent Antibody Response

Antibody status: ND = Not Detected; NT = No Test

Anti-LY296316 Cross Reactivity: CR = Cross Reactive; NT = No Test; NCR = Not Cross Reactive.

Reviewer's Comment: The Sponsor confirmed that any patient who had the presence of antidrug antibody for at least 1 time point during the course of the study independent of baseline status was reported as antibody positive. The data indicated that in ABEB studies (T1DM, 52 weeks), similar percent (42%) of subjects were ADA+, treated either with LY2963016 or LANTUS®).

Similarly, in ABEC (T2DM, 24 weeks) studies, overall number of patients with detectable antibodies to insulin LY2963016 were 15.8% (n=60/379) of the treatment in contrast to 13.1% patients (n=48/365) treated with LANTUS® including those who were baseline positive for ADA but did not significantly change the antibody binding in the assay over the course of the studies. The difference (2.7%) may be attributed to the 5.5%, baseline positive patients enrolled for the study treated with LY2963016 compared to 3.6% to LANTUS® respectively.

Appendix 2:**References:**

Home PD, Roskamp R, Forjanic-Klapproth J, Dressler A, on behalf of the European Insulin Glargine Study Group. A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes. *Diabetes Metab Res Rev.* 2005;21(6):545-553.

Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA, for the US Study Group of Insulin Glargine in Type 1 Diabetes. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care.* 2000;23(5):639-643.

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/s/

FARUK G SHEIKH
07/10/2014

DANIELA I VERTHELYI
07/10/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 23, 2014

TO: Callie Cappel-Lynch, Regulatory Project Manager
Lisa Yanoff, M.D., Medical Officer
Ali Mohamadi, M.D., Team Leader
Division of Metabolism and Endocrine Products

FROM: John Lee M.D., Medical Officer
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
Kassa Ayalew, M.D., Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 205692

APPLICANT: Eli Lilly and Company

DRUG: Insulin glargine (pending trade name, (b) (4) KwikPen®)

NME: No

INDICATION: Glycemic control in diabetes mellitus

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: January 6, 2014

INSPECTION SUMMARY GOAL DATE: June 23, 2014

REGULATORY ACTION GOAL DATE: August 18, 2014

PDUFA DUE DATE: August 18, 2014

I. BACKGROUND

Eli Lilly and Company (**Lilly**) submits this NDA 205-692 under section 505(b)(2) of the Food Drug and Cosmetic Act (**FDCA**) for (b)(4) KwikPen[®] (LY2963016), as previously discussed with the FDA under IND 105423. The same indication is being sought as for the listed (approved) reference drug LANTUS[®]; this NDA relies on the previous finding of safety and efficacy of the reference drug and two studies (described below) in which the study medication was compared to the reference drug.

(b)(4) is a long-acting human insulin analog with the proposed indication of improved glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. This product has been developed in collaboration with Boehringer Ingelheim (**BI**) and is intended to be marketed by BI as well as by Lilly. (b)(4)

(b)(4) KwikPen[®] is manufactured as a 3-mL prefilled pen injector for subcutaneous (**SC**) injection to deliver the active ingredient at a concentration of 100 units per mL. (b)(4) KwikPen[®] is similar to the 3-mL cartridge presentation of LANTUS SoloSTAR[®]. The product was developed under the name LY2963016.

Study 14L-MC-ABEC

A Prospective, Randomized, Double-Blind Comparison of a Long-Acting Basal Insulin Analog LY2963016 to LANTUS[®] in Adult Patients with Type 2 Diabetes Mellitus (ELEMENT 2 Study)

This Phase 3, randomized, double-blind, 24-week study was conducted over 12 months (September 2011 to September 2012) at 88 sites in 13 countries in 759 subjects (379 LY2963016, 380 LANTUS[®]) with type 2 diabetes mellitus (**T2DM**), of whom 662 subjects (334 LY2963016, 328 LANTUS[®]) completed 24 weeks of treatment. The primary objective was to show that LY2963016 administered once daily (**QD**) was not inferior to LANTUS[®] administered QD when used to initiate insulin therapy in combination with oral anti-hyperglycemic medications (**OAMs**). The primary efficacy variable was the change in hemoglobin A1c (**HbA1c**) from baseline to 24 weeks.

Subject Inclusion

- T2DM based on the diagnostic criteria described by the World Health Organization (**WHO**)
- 18 years of age or older with a body mass index of $\leq 45 \text{ kg/m}^2$
- Prior stable therapy with two or more OAMs for 12 weeks or longer (with or without LANTUS[®])
- HbA1c $\geq 7.0\%$ and $\leq 11.0\%$ if insulin naive, or an HbA1c $\leq 11.0\%$ if previously on LANTUS[®]
- Willing to perform SMBG and complete diary as required
- Able to use insulin vial and syringe according to study instructions and receptive to diabetes education

Subject Exclusion

- Use of any insulin except LANTUS[®] within 90 days, including any human insulin or insulin analog
- Prior exposure to a biosimilar insulin glargine within the previous 90 days
- History of basal bolus therapy or need for mealtime insulin to achieve target control
- Prior use of short-acting glucagon like peptide (GLP-1) agonist within 30 days
- Prior use of pramlintide within 30 days
- Have excessive insulin resistance at study entry (total insulin dose $\geq 1.5 \text{ U/kg}$)
- Have had more than one episode of severe hypoglycemia within 6 months
- Known hypersensitivity or allergy to LANTUS[®] or its excipients
- Chronic (> 14 consecutive days) systemic glucocorticoids within 4 weeks
- Evidence of liver disease (abnormal albumin or alanine/aspartate aminotransferase > 2.5 normal)
- Any significant cardiac or gastrointestinal disease
- History of renal transplantation, current dialysis or serum creatinine $> 2.0 \text{ mg/dL}$
- History of blood transfusion or severe blood loss within three months
- Known hemoglobinopathy, hemolytic anemia, or sickle cell anemia

- Invasive (carcinoma in situ excluded) cancer within five years (except basal cell carcinoma)
- Lilly employees or site personnel directly affiliated with this study or their immediate families
- Any condition (e.g., drug/alcohol abuse) that precludes successful study completion
- Participation within 30 days in an investigational drug/device study (other than LY2963016)
- Previously completed or withdrawn from this study

Treatment Groups and Regimen

- Test group, (b) (4)
 - Previous LANTUS[®]: LY2963016 QD SC starting dose equivalent to pre-study LANTUS[®] dose, then titrated to maintain non-hypoglycemic fasting blood glucose (FBG) ≤ 100 mg/dL
 - Insulin naive: LY2963016 QD SC starting dose of 10 U, then titrated to maintain non-hypoglycemic FBG ≤ 100 mg/dL
- Reference group, LANTUS[®]
 - Previous LANTUS[®]: LANTUS[®] QD SC starting dose same as the pre-study dose, then titrated to maintain non-hypoglycemic FBG ≤ 100 mg/dL
 - Insulin naive: LANTUS[®] QD SC starting dose of 10 U, then titrated to maintain non-hypoglycemic FBG ≤ 100 mg/dL

Major Endpoints

- Primary efficacy: Change in HbA1c from baseline to Week 24 (or last post-baseline observation carried forward, LOCF)
- Major secondary efficacy:
 - Self-monitored blood glucose (SMBG), 7-points throughout day (over 24 hours)
 - Intra-subject variability as measured by the standard deviation (SD) of FBG
 - Change in HbA1c from baseline to 4, 8, 12, 16, 20 and 24 weeks (LOCF)
 - Percentage of subjects achieving HbA1c targets ($< 7\%$, $\leq 6.5\%$)
 - Basal insulin dose and body weight at end of treatment
- Major safety endpoints:
 - Adverse events (AEs) including abnormal vital signs and serious AEs (SAEs)
 - Hypoglycemic events (total, severe, nocturnal, symptomatic, unspecified)
 - Laboratory measures including insulin antibodies (% binding)
 - Discontinuation from study due to one or more AEs
 - Insulin Treatment Satisfaction Questionnaire (ITSQ)
 - Adult Low Blood Sugar Survey (ALBSS)

Major Sponsor Reported Findings

- Efficacy (mean exposure of 22 weeks for both groups)
 - Significant ($p < 0.001$) reductions in HbA1c from baseline to endpoint (LOCF) for both groups
 - LY2963016 not inferior to LANTUS[®] for the primary endpoint at 0.3% non-inferiority margin
 - Least squares (LS) mean difference (test - control) = 0.052% (-0.070 - 0.175, 95% confidence)
 - LY2963016 not inferior to LANTUS[®] for the major secondary endpoints
- Safety: similar findings for both groups, no new safety findings in either group
 - Two deaths (LY2963016, lung adenocarcinoma; LANTUS[®], myocardial infarction)
 - Most frequent SAE: severe hypoglycemia in five subjects (two LY2963016, three LANTUS[®])
 - Nine subjects discontinued due to SAE (four LY2963016, five LANTUS[®])

Study 14L-MC-ABEB

A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to LANTUS[®] in Combination with Mealtime Insulin LISPRO[®] in Adult Patients with Type 1 Diabetes Mellitus (ELEMENT 1 Study)

This Phase 3, randomized, open-label study was conducted over 18 months (September 2011 to March 2013) at 59 sites in 9 countries in 536 subjects (269 LY2963016, 267 LANTUS[®]) with type 1 diabetes mellitus (**T1DM**), of whom 509 subjects (253 LY2963016, 256 LANTUS[®]) completed 24 weeks of treatment and 490 subjects (245 LY2963016, 245 LANTUS[®]) completed 52 weeks (28-week extension and 4-week post-treatment follow-up). The primary objective was to show that LY2963016 administered QD was not inferior to LANTUS[®] administered QD when used in combination with pre-meal insulin LISPRO[®] administered three times per day (**TID**). The primary efficacy variable was the change in HbA1c from baseline to 24 weeks.

Subject Inclusion

- T1DM based on the diagnostic criteria described by WHO, disease duration \geq one year
- 18 years of age or older with a body mass index of $\leq 35 \text{ kg/m}^2$ and HbA1c $\leq 11.0\%$
- Basal-bolus insulin therapy for \geq one year
- Willing to perform SMBG and complete diary as required
- Able to use insulin vial and syringe according to study instructions
- Receptive to diabetes education

Subject Exclusion

- Exposure to a biosimilar insulin glargine
- Excessive insulin resistance at entry into the study (total daily insulin dose $\geq 1.5 \text{ U/kg}$)
- Have had more than one episode of severe hypoglycemia within six months
- Prior diabetic ketoacidosis
- Uncontrolled diabetes requiring hospitalization within six months
- Known hypersensitivity or allergy to any of the insulin study medications or excipients
- Pregnant, intent to become pregnant during study, or sexually active
- Women of childbearing potential not practicing acceptable birth control
- Breastfeeding
- Have taken any oral anti-hyperglycemic medication (**OAM**) within three months
- Treatment within last 30 days with a drug that has not received regulatory approval
- Treatment with pramlintide or with continuous SC insulin infusion within three months
- Irregular sleep/wake cycle (e.g., work during night)
- Chronic (>14 consecutive days) systemic glucocorticoids within 4 weeks
- Evidence of liver disease
- Abnormal albumin or alanine/aspartate aminotransferase > 2.5 normal
- Any significant cardiac or gastrointestinal disease
- History of renal transplantation
- Current dialysis or serum creatinine $> 2.0 \text{ mg/dL}$
- History of blood transfusion or severe blood loss within three months
- Known hemoglobinopathy, hemolytic anemia, or sickle cell anemia
- Invasive (carcinoma in situ excluded) cancer within five years (except basal cell carcinoma)
- Lilly employees or site personnel directly affiliated with this study or their immediate families
- Any condition (e.g., drug/alcohol abuse) that precludes successful study completion
- Participation within 30 days in an investigational drug/device study (other than LY2963016)
- Previously completed or withdrawn from this study after signing the informed consent document

Treatment Groups and Regimen

- LY2963016 QD: started at same dose and schedule (time of day) as pre-study QD basal insulin
 - LISPRO[®] given with meals at same dose as pre-study mealtime insulin
 - Basal and bolus insulin doses titrated to achieve glycemic targets: HbA1c < 7%, fasting plasma-equivalent glucose (FPG) ≤ 108 mg/dL, other preprandial capillary blood glucose 70-130 mg/dL, and no hypoglycemia
- LANTUS[®] QD: started at same dose and schedule (time of day) as pre-study QD basal insulin
 - LISPRO[®] given with meals at same dose as pre-study mealtime insulin
 - Basal and bolus insulin doses titrated to achieve glycemic targets: HbA1c < 7%, FPG ≤ 108 mg/dL, other preprandial capillary blood glucose 70-130 mg/dL, and no hypoglycemia

Major Endpoints

- Primary efficacy: Change in HbA1c from baseline to Week 24 (LOCF)
- Major secondary efficacy:
 - Change in HbA1c from baseline to Weeks 6, 12, 24, 36, and 52 (LOCF)
 - Seven-point SMBG throughout day (over 24 hours)
 - Intra-subject variability as measured by SD of FBG
 - Percentage of subjects achieving HbA1c targets (< 7%, ≤ 6.5%)
 - Within and between-day blood glucose (BG) variability
 - Within-subject, within-day BG variability
 - Basal, LISPRO[®], and total insulin dose at end of study
 - Weight and body mass index (BMI) at end of study
- Major safety endpoints:
 - AEs, including abnormal vital signs
 - Hypoglycemic events (total, severe, nocturnal, symptomatic, unspecified)
 - Discontinuation from study due to one or more AEs
 - Laboratory measures including insulin antibodies (% binding)
 - ITSQ and ALBSS

Major Sponsor Reported Findings

- Efficacy (mean exposures: 49 weeks LY2963016, 50 weeks LANTUS[®])
 - Significant ($p < 0.001$) reductions in HbA1c from baseline to 24 and 52 weeks for both groups
 - LY2963016 not inferior to LANTUS[®] for the primary endpoint at 0.3% non-inferiority margin
 - LS mean difference (LY2963016 - LANTUS[®]) = 0.108% (-0.002% to 0.219% 95% confidence)
 - LY2963016 not inferior to LANTUS[®] for the major secondary endpoints
 - No significant differences between treatment groups for ITSQ or ALBSS
- Safety: similar findings for both groups, no new safety findings in either group
 - One death (LANTUS[®], hypertrophic cardiomyopathy)
 - SAE in 52-week study: 44 (8.2%) subjects, 20 (7.5%) for LY2963016, 24 (9.0%) for LANTUS[®]
 - Most frequent SAE: severe hypoglycemia in 25 subjects (13 LY2963016, 12 LANTUS[®])
 - Six subjects discontinued due to SAE (one LY2963016, five LANTUS[®])
 - Eight subjects discontinued due to AE (two LY2963016, six LANTUS[®])
 - No significant differences between groups for overall incidence and rate of hypoglycemia

III. INSPECTIONS

The following clinical investigator sites were selected for inspection based primarily on large subject enrollment, participation in both Studies 14L-MC-ABEB and 14L-MC-ABEC, and: (1) for Bhargava, relatively high SAE rate for Study 14L-MC-ABEC and all screened subjects enrolled (no screen failures) in Study 14L-MC-ABEB; and (2) for Reed, unbalanced randomization ratio of 2/15 (test subjects/control subjects) for Study 14L-MC-ABEB.

Clinical Investigator Site		Study, Site, Enrollment	Inspection Dates and Outcome
1	Anuj Bhargava, M.D. Des Moines, IA	I4L-MC-ABEB, Site 008, 30 subjects I4L-MC-ABEC, Site 010, 22 subjects	February 11 – 18, 2014 VAI
2	John Reed, M.D. Roswell, GA	I4L-MC-ABEB, Site 100, 17 subjects I4L-MC-ABEC, Site 116, 15 subjects	April 8 – 16, 2014 pending, preliminary NAI

NAI = no action indicated (no significant GCP deviations); VAI = voluntary action indicated (significant GCP deviations); OAI = official action indicated (serious GCP deviations and/or data unreliable)

Pending: Preliminary classification is based on information on Form FDA 483 and preliminary communication with the field investigator. The final establishment inspection report (**EIR**) has not been received from the field office and OSI's review of the final EIR remains pending as of this clinical inspection summary (**CIS**).

1. Anuj Bhargava, M.D.

- a. What was inspected: Compliance with study protocols, good clinical practice (**GCP**) regulations, and standard operating procedures (**SOPs**)
 - Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records for data verification
 - Data verification: subject eligibility, informed consent, subject randomization, study blind, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
 - Study I4L-MC-ABEB: 30 subjects were screened, 30 were enrolled, and 27 completed the study. Subject records were completely reviewed for 11 subjects.
 - Study 14L-MC-ABEC: 27 subjects were screened, 22 were enrolled, and 20 completed the study. Subject records were completely reviewed for 11 subjects.

b. General observations and comments:

A Form FDA 483 was issued for minor record keeping deficiencies about drug handling and accountability for Study 14L-MC-ABEC. Specifically:

- Receipt of Order 177188 was documented on March 22, 2012 as having been received on March 5, 2012. The drug product was made available in IVRS on March 8, 2012.
- Receipt of Order 168431 was documented on March 22, 2012 as having been received on January 16 2012. The drug product was made available in IVRS on January 16, 2012.

Other minor findings (not cited) included one isolated unreported adverse event for one subject, tingling in arms and legs for several days (resolved without intervention). All deficiency

findings (cited and not cited) appeared minor, isolated, and unlikely to have affected the study data. The study conduct at this site was otherwise GCP-compliant. Study monitoring appeared to be adequate. All subjects signed the informed consent document. Source records appeared complete. There was no evidence of under-reporting of adverse events. Audited endpoint data matched between source records, case report forms, and NDA data listings.

Reviewer Comments: This site was noteworthy (pre-audit) for relatively high SAE rates for both studies and no screen failures (all screened subjects enrolled) in Study 14L-MC-ABEB. GCP violations potentially related to these pre-audit concerns were not observed. The relatively high SAE rates may (or may not) reflect diligent AE monitoring and reporting; evidence of inadequate subject safety monitoring was not observed. Screen failure rates tended to be low (all sites, both studies); there was no evidence of inadequate screening for Study 14L-MC-ABEB at this site.

- c. Assessment of data integrity: Data from this study site appear reliable.

Note: In the internal note to the review division for the April 29, 2014 letter to the clinical investigator, the numbers of subjects at this site for Study 14L-MC-ABEC were reported incorrectly as 32 screened and 27 enrolled. The correct numbers are 27 screened and 22 enrolled, as shown above. The letter sent to clinical investigator did not contain this error; an addendum to correct the error will not be issued.

2. John Reed, M.D.

- a. What was inspected: Compliance with study protocols, GCP regulations, and SOPs
- Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records for data verification
 - Data verification: subject eligibility, informed consent, subject randomization, study blind, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
 - Study I4L-MC-ABEB: 19 subjects were screened, 17 were enrolled, and 16 completed the study. Subject records were completely reviewed for 8 subjects.
 - Study 14L-MC-ABEC: 22 subjects were screened, 15 were enrolled, and 7 completed the study. Subject records were completely reviewed for 10 subjects.
- b. General observations and comments:

No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared adequate. All subjects signed the informed consent document. Drug accountability was well documented. Source records appeared complete. There was no evidence of underreporting of adverse events. Audited endpoint data matched among source records, case report forms, and NDA data listings.

Reviewer Comments: This site was noteworthy (pre-audit) for an unbalanced randomization ratio of 2/15 (test/control) for Study 14L-MC-ABEB. Potentially related GCP violations were not observed; the unbalanced randomization appears to be a chance event, given the many stratification variables including baseline HbA1c level and medication injection time of day.

- c. Assessment of data integrity: Data from this study site appear reliable.

Note: These observations are based on preliminary communications with the field investigator. The final inspection report has not been received and the inspection outcome remains pending.

IV. OVERALL ASSESSMENT AND RECOMMENDATIONS

Under FDCA 505(b)(2), Lilly seeks approval of (b) (4) KwikPen[®] (insulin glargine), a long-acting human insulin analog for use in improving glycemic control in diabetes mellitus. Lilly sponsored two new studies to compare the study medication with an approved reference drug. Both studies were audited at clinical inspections of two study sites; both sites were selected for participation in both studies and large subject enrollment. Both study sites were found to be GCP-compliant; all findings (cited and not cited) were limited to minor isolated deficiencies unlikely to have a significant impact on the study outcome. The data from the inspected study sites appear reliable.

Note: For one site (Reed), the final EIR has not been received from the field office and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communications with the field investigator. An addendum to this CIS will be forwarded to the review division if the final outcome classification changes or if any observations of clinical or regulatory significance are discovered upon receipt and review of the final EIR.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
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/s/

JONG HOON LEE
06/23/2014

JANICE K POHLMAN
06/23/2014

KASSA AYALEW
06/23/2014

Date: June 12, 2014
From: Lening Shen, WO66, RM 2558
General Hospital Devices Branch, DAGRID, ODE, CDRH
To: Callie Cappel-Lynch, DMEP/CDER
Subject: CDRH Consult, ICC1300540, NDA 205692, Eli Lilly and Company
LY2963016 KwikPen™ (LY2963016 KP)
Consultants: Bifeng Qian, MD, Ph.D, CDRH/ODE/DAGRID/INCB

1. Issue

This consult is to review information provided by the sponsor to assure reasonable safe and effective device performance (Sterility, Biocompatibility and Bench) review on the device of the submission.

In (b) (4), the sponsor has provided responses to information the Agency requested in (b) (4). Please refer to Section 4 below for details.

2. Documents Reviewed

Section 3.2.R.3 (medical-device.pdf)

Additional information provided based on inquiry of original consult review. Email received on December 17, 2014.

The sponsor provided the following description of the device.

The information in Section 3.2.P.7 includes the description and controls for the LY2963016 drug product multi-dose cartridge container closure system.

The drug product is filled into a Type 1 glass cartridge. The cartridge is sealed with a (b) (4) disc seal and with a gray (b) (4) plunger. The following table provides the descriptions for the primary packaging components.

Table 3.2.P.7.2-1 Package Size and Description for Container Closure System

Drug Product Strength (U/mL)	Cartridge Size	Packaging Components and Identification
100	3 mL	<u>Primary Components</u> Cartridge: Type I clear glass. Disc Seal: [REDACTED] (b) (4) [REDACTED] (b) (4) Plunger: [REDACTED] (b) (4) [REDACTED] (b) (4)



The sponsor referred to the following standards:

Table 3.2.P.7.4-1 Compendial References for Primary Packaging Components

Packaging Component	Relevant Standard
Cartridge	The glass cartridges comply with applicable limits for Type 1 glass in USP <660>, Containers – Glass.
Disc Seal	The elastomeric disc complies with requirements for Type 1 elastomeric closures in USP<381>, Elastomeric Closures for Injections.
Plunger	The elastomeric plunger complies with requirements for Type 1 elastomeric closures in USP<381>, Elastomeric Closures for Injections.

3. CDRH Review and Comments

The sponsor has provided Sterility, Biocompatibility, and Bench performance test reports.

Clinical

Dr. Patricia Beaston reviewed the summary data and concluded that the sponsor has submitted adequate information for her to conduct a clinical review of the device component. The Sponsor is proposing an insulin glargine 505(b)(2) under the trade name (b) (4). The dose accuracy performance meets requirements. She believes that no new clinical issues were identified for the device component of this combination product.

Sterility

R. Kapil Panguluri, Ph.D. of INCB reviewed the sterility information provided by the sponsor. The sponsor stated that the LY2963016 KwikPen is not a sterile device; therefore there is no sterility report. The device components of the KwikPen do not need to be sterilized because the components of the pen-injector do not contact the drug product. The drug product is contained in its primary container closure (cartridge) and the fluid path into the body is through an attached, disposable, single-use sterile needle. The needle is not supplied by Lilly; it is purchased separately by the user. There are no concerns about interaction between the drug product and the device components because there is no contact between these components.

Based on the information provided, the drug is enclosed in a cartridge and the material of which has not been changed in this present sub. The only portion that was changed is the plunger which does not come in contact with the patient or the drug. Hence, R. Kapil Panguluri, Ph.D. of INCB agrees with the firm's response that the sterility is not required as the change in plunger material does not contact the drug cartridge.

Biocompatibility

The sponsor stated that a biological evaluation was performed on the KwikPen platform of devices in accordance with ISO 10993-1:2009. This evaluation included the currently marketed version of KwikPen and versions under evaluation by regulatory agencies. The LY2963016 device is included in the scope of this evaluation as documented in PDS-

REPORTS-01696 *Biological Evaluation of KwikPen Device Platform*. Section 7 of the report concluded that:

“KwikPen is classified as a limited duration skin contact device. Users of the device hold it in their hands for a minute or two a few times per day. The risk to the user is low based on the limited contact. The plastic materials used in the device are well understood by their manufacturers and have been used for several years by Lilly. The analysis referred to in this report has been reviewed by Lilly corporate toxicologist who has confirmed that the plastic materials used in the KwikPen platform have been evaluated according to the guidance in ISO 10993-1 and pose no additional risk to patient safety.”

Rakhi Dalal, Ph. D. of GHDB reviewed the information submitted by the sponsor and believed that they are deficient. It appears that there are several configurations of Kwik Pen. Also, there may be other modification eliciting Human factor review of the dose-color identification. In regards to biocompatibility, in the submission only biocompatibility of Kwik Pen material of construction for the LY2963016 cartridge holder is provided. As FDA clears/approves medical devices and biocompatibility assessments are used for analyzing post manufacturing residuals and not the raw materials used in construction, she listed two deficiencies regarding found in this submission below.

Bench

The sponsor stated that the design verification testing in accordance with ISO11608-1:2012 was performed using preapproved protocol PDS-PROTOCOLS-00336 *KwikPen* (b) (4) *ISO11608-1 Design Verification Test Protocol*. The results of the ISO11608 testing along with Lilly specific testing are included in PDS-REPORTS-01164 (b) (4) *Design Verification Technical Report*. Section 10 of the report concluded that:

“The (b) (4) Design Verification Builds, PDS Lots #12220-001 and 12299-001 met all design verification acceptance criteria for ISO11608-1:2012, per PDS-PROTOCOLS-00336. The design also meets design verification acceptance criteria for Lot Release Dose Accuracy per PDS-00011-LOCAL-NC and Functional Attributes Testing per PDS-PROTOCOLS-00252.

Therefore, the design output for the KwikPen (b) (4) device meets the design input requirements tested.”

The protocol and technical report are provided in the response to our questions. The sponsor indicated that all tests pass.

However, for the glass cylinder, the sponsor has not provided performance testing information, such as for the cylinder or the plunger. We recommend that the sponsor provide this information based on ISO 13926-1 and -2.. The sponsor has provided these test reports in (b) (4) and all test passed acceptance criteria and therefore, this issue is resolved.

4. CDRH Recommendation – for (b) (4) (sent to CDER on March 13, 2014)

CDRH/ODE initially recommends the following deficiencies to be relayed to the NDA sponsor on 3/13/2014:

1. In NDA 205692 you have indicated that the LY2963016 will be made available in a 3 mL cartridge sealed in a prefilled pen injector (KwikPen™). The submission indicates that changes with regards to pen injector was made, i.e., the plunger component which can impact the patient safety. Please provide the side-by-side comparison of the previous KwikPen device and the new and modified KwikPen in terms of design, patient/drug contacting device components, materials used in manufacturing including (b) (4) of the new prefilled pen injector (KwikPen™). Information in regards to the device is limited.

Sponsor's Response (b) (4) :

The LY2963016 KwikPen shares the same dosing mechanism with the currently marketed Humalog KwikPen (NDA20563). A side-by-side comparison of the LY2963016 KwikPen and the Humalog KwikPen is shown in Figure Q.3-2 to illustrate the design improvement. Table Q.3-1 depicts the side-by-side comparison of the LY2963016 KwikPen and the Humalog KwikPen for the patient/drug contacting device components that include the materials used in manufacturing including (b) (4) used in the process.

Reviewer's Note (b) (4) :

Bifeng Qian, MD, PhD review the response provided by the sponsor and has the following comments:

It appears that several new materials have been introduced in the patient/drug contacting components of the LY2963016 KwikPen that is proposed in NDA 205692, including the new colorants, inks, etc. Recommend that the sponsor identify the chemical identity, composition, health problems associated with the chemical, and toxicological data (reference doses, LD₅₀, NOAEL, and LOAEL), for each of the new materials used in the patient/drug contacting device components of the LY2963016 KwikPen. This information may be contained in the Material Safety Data Sheets (MSDS) or Technical Specification Sheets.

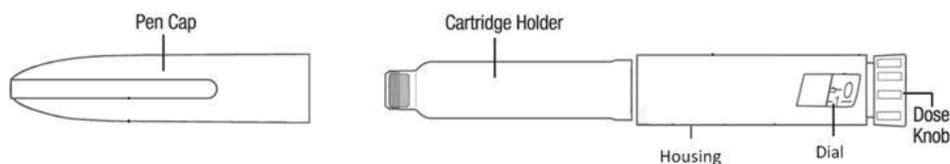
I concur with her findings and request this deficiency to be relayed to the sponsor.

2. Page 44/171 states “KwikPen is classified as a limited duration skin contact device. ... plastic materials used in the KwikPen platform have been evaluated according to the guidance in ISO 10993-1”. As FDA clears or approves medical devices and biocompatibility assessments in medical device applications are considered for evaluating post-manufacturing residuals in the final finished device, limitations apply

when utilizing raw material biocompatibility for medical product clearance or approval. Based on the identified classification, please provide complete biocompatibility study reports for FDA evaluation. If you have leveraged the biocompatibility studies based on existing predicate device or have submitted the reports elsewhere in the submission, you may provide the information for evaluation.

Sponsor's Response (b) (4) :

Lilly has reviewed the FDA guidance, Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'. Lilly will conduct the biocompatibility testing of Cytotoxicity, Sensitization, and Irritation in both polar and non-polar test extracts on the molded plastic patient contact parts of the final finished devices shown in the illustration below.



The results of the Cytotoxicity and Irritation testing (3-4 week test) will be provided to the FDA as they become available. The Sensitization data will also be provided to the FDA at the completion of the 9 week test.

Note: The Rubber Disc Seal in the 3 mL cartridge is used in Lilly commercial insulin formulations and has been approved by the FDA as a component of the primary drug container closure for the Lilly's Humulin and Humalog drug products (NDA 18-781, NDA 19-717, NDA 20-563, NDA 21-017, and NDA 21-018) and Forteo® (NDA 21-318).

Reviewer's Note (b) (4) :

Bifeng Qian, MD, PhD review the response provided by the sponsor and has the following comments:

In this supplement response, the sponsor states that they will conduct the biocompatibility testing based on the current FDA guidance. However, the complete biocompatibility testing reports have not been provided for review. The deficiency remains.

I concur with her findings and request this deficiency to be relayed to the sponsor.

3. In your submission, we cannot locate performance testing information on your glass cylinder and the enclosed plunger. We recommend that you follow ISO 13926-1 and ISO 13926-2 when conducting your performance testing. Please provide us your reports including test protocol, test data, pass/fail criteria, and test results.

Sponsor's Response (b) (4) :

In the file “1111-quality-response-to-question-may-2014.pdf”, the sponsor has provided summary test reports for both the glass cartridge and the plunger according to ISO 13926-2. This information including test protocols, test data, acceptance criteria and test results. Test results indicate that the device meets requirements of ISO13296-2.

Reviewer’s Note (b) (4) :

Adequate information provided by the sponsor. I have no further issues.

5. Recommended Deficiencies to the Sponsor (b) (4)
ICC1300540/ (b) (4) - Deficiencies

NOTE TO CDER: It is recommended that CDER/DMEP Pharmtox reviewer verify that toxicology of leachable / extractable emanating from device constituents have been adequately addressed within the NDA. Alternatively, CDRH proposes the following deficiency regarding toxicology of device constituent materials contacting the drug.

1. It appears that several new materials have been introduced in the patient/drug contacting components of the LY2963016 KwikPen that is proposed in NDA 205692, including the new colorants, inks, etc. Please identify the chemical identity, composition, health problems associated with the chemical, and toxicological data (reference doses, LD₅₀, NOAEL, and LOAEL), for each of the new materials used in the patient/drug contacting device components of the LY2963016 KwikPen. This information may be contained in the Material Safety Data Sheets (MSDS) or Technical Specification Sheets.

CDRH Recommends the following deficiency to assure biocompatibility of skin contacting materials has been addressed.

2. In this supplement response, you state that you will conduct the biocompatibility testing based on the current FDA guidance. However, you have not provided any biocompatibility testing reports for review. As we have previously requested, please provide complete biocompatibility study reports of the following based on the final finished subject device and a worst case condition:
 - a. *In vitro* cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for *in vitro* cytotoxicity;
 - b. Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
 - c. Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization.

Digital Signature Concurrence Table

Reviewer Sign-Off	Lening Shen - S  Digitally signed by Lening Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lening Shen -S, 0.9.2342.19200300.100.1.1=1300435455 Date: 2014.06.12 15:17:33 -04'00'
Combination Product Team Lead Sign-Off	Alan M. Stevens -S Date: 2014.06.12 15:29:48 -04'00'
Branch Chief Sign-Off	 Digitally signed by Richard C. Chapman -S Date: 2014.06.12 15:32:52 -04'00'

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

/s/

CALLIE C CAPPEL-LYNCH

06/12/2014

signed for lening shen

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*****

Date of This Review: April 8, 2014
Requesting Office or Division: Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number: NDA 205692
Product Name and Strength: Basaglar (insulin glargine [rDNA origin]) injection,
100 units/mL
Product Type: Combination (drug + device)
Rx or OTC: Rx
Applicant/Sponsor Name: Eli Lilly and Co.
Submission Date: October 17, 2013
OSE RCM #: 2013-2416 & 2423
DMEPA Primary Reviewer: Sarah K. Vee, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

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 Basaglar (insulin glargine [rDNA origin]), to ensure the intended population is able to use the product safely and effectively. This NDA is submitted as a 505(b)(2).

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.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	N/A
Human Factors Study	B
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The use errors reported in the human factors study results do not present an approval issue for the proposed pen. Errors that occurred in the priority task of select/differentiate were an artifact of the study design. The 8 patients (all insulin experienced) who chose the wrong pen in 1 or 3 of the scenarios stated that they did not understand the purpose of the differentiation task, chose their own pen, or chose the pen that was appealing to them. Most of them selected the pens prior to receiving the task instructions.

Dialing the dose and delivering the dose are common tasks for all insulin pen injectors and errors occurring during those tasks can be attributed to participants' inattention to the task, thus not attributable to the product design of the proposed pen. We also note that the KwikPen prefilled pen platform for the proposed product is already approved for other insulin products marketed by the Applicant (e.g., Humalog Kwikpen, Humulin 70/30 Kwikpen, Humulin

N Kwikpen), and that no significant safety issues have been reported with this device post approval.

4 CONCLUSION & RECOMMENDATIONS

The Human Factors Study demonstrated that users are able to use prefilled pen safely and effectively. As a result, DMEPA concludes that with minor revisions to the pen label and carton labeling, patients can safely and effectively use the proposed prefilled pen.

The proposed container label, carton 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 NDA:

4.1.1 Pen Label

- A. 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.

4.1.2 Carton Labeling

- A. See 4.1.1 A
- B. Add “For Single Patient Use Only” to the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Basaglar that Lilly submitted on October 17, 2013.

Table 2. Relevant Product Information for Basaglar			
Active Ingredient	Insulin glargine [rDNA origin]		
Indication	Improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.		
Route of Administration	Subcutaneous injection		
Dosage Form	Solution		
Strength	100 units/mL		
Dose and Frequency	Individualized dose once daily		
How Supplied	Prefilled Pen 5 x 3 mL		
Storage	Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, (Below 86°F [30°C])
	28 days	Until expiration date	28 days, Do not refrigerate.
Container Closure	The drug product is filled into a Type 1 glass cartridge. The cartridge is sealed with a (b) (4) disc seal and with a gray (b) (4) plunger.		

APPENDIX B. HUMAN FACTORS STUDY

B.1 Study Design

Study Participants

None of the HCP subjects received training on the use of the device as this was deemed representative of real world use for these users. Per the protocol, all non-HCP subjects enrolled and assigned to the training arm were provided one-on-one training by the moderator on the proper use of the (b) (4) KwikPen device, utilizing the IFU as a training resource. Training was designed to simulate the typical device instruction a patient who is new to insulin or pen injectors might receive.

The training sessions consisted of:

- Injection demonstration by Trainer (Moderator) per Instructions for Use.
- Injection Demonstration by Respondent with correction or coaching by the trainer as necessary for the respondent to perform the task correctly per Instructions for Use.

The training sessions lasted approximately 20 minutes, depending on the number of questions asked by the respondent. After the training session, subjects left the interview room for a training decay period of at least one hour with a maximum decay of 4:35. This was done to reflect the time between receiving training at a clinic or doctor's office and then performing an injection at home.

Table 6-3: Patient/Caregiver Stratification

User Group	Insulin naive	Insulin experienced	Lantus Users	Caregiver	Total for impairments
No impairment	11	16	13	16	56
Vision Impairment only*	1	6	1	1	9
Vision and Hand	3	5	2	0	10
Hand Impairment only**	5	2	2	0	9
Colorblind****	4	6	3	1	14
Total for user groups	20	29	18	17	84

6.6.2.3. HCP Demographics

All of the demographic criteria for the nurse, pharmacist, and physician populations were fulfilled. The 18 HCP participants included:

- 2 Diabetes Educators
- 3 RN
- 3 Pharmacists
- 2 Endocrinologists
- 5 Primary Care
- 3 Nurse Practitioners

Study Protocol

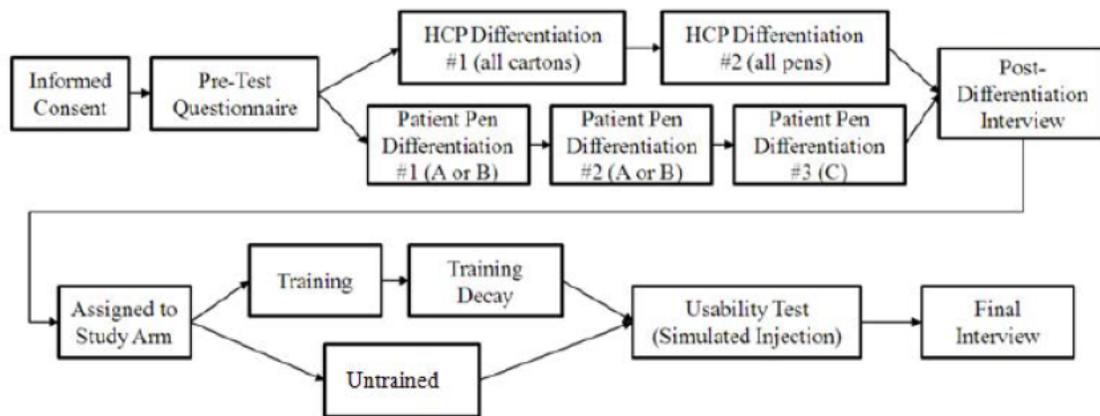


Figure 12 (b) (4) Summative Human Factors Study Flow

Table 6-6: Non-HCP Differentiation Scenarios

Scenario A: Subject must choose the right pen from the following:	Scenario B: Subject must choose the right pen from the following:	Scenario C: Subject must choose the right pen from the following:
(b) (4) KwikPen Humulin N KwikPen Humalog KwikPen Humalog 600 Unit KwikPen	(b) (4) KwikPen Apidra® SoloSTAR® NovoLog® FlexPen®	(b) (4) KwikPen Lantus® SoloSTAR®

(b) (4) **HCP Differentiation Tasks:** It is reasonably foreseeable that an HCP would need to identify the (b) (4) KwikPen when presented with many more devices and/or cartons of devices. Each HCP was provided with all devices listed and asked to differentiate among them. The HCP differentiation scenario was separated into two tasks. In the first task, each HCP was asked to select the (b) (4) carton. For the second differentiation task, each HCP was asked to select the (b) (4) pen.

Critical/Priority Tasks

Priority Task	Definition of Success
<i>Select / Differentiate</i>	Correct pen was selected after scenario given
<i>Dial the Dose</i>	Correct number of units dialed per written prescription given to subject
<i>Deliver the Desired Dose</i>	Dial returned to zero

B.2 Results

Table 6-7: Overall Completion Rates for Priority Tasks

Priority Task Completion	Select / Differentiate	Dial the Dose	Deliver the Desired Dose
Non-HCP	Scenario A: 95% (80/84) Scenario B: 94% (79/84) Scenario C: 95% (80/84)	96% (81/84)	94% (79/84)
HCPs	Carton 89% (16/18) Pen 94% (17/18)	100% (18/18)	78% (14/18)

B.2.1 Select/Differentiate:

Table 6-8 Demographics for Select / Differentiation Errors

#	Demographics								Differentiation Scenario and Pen Chosen				Analysis
	Quota Segment	Pen, Vial Syringe	Age	Gender	Type of Diabetes	Hand Impairment	Eye Impairment	Colorblind	Order	A	B	C	
6	Insulin Experienced	Vial Syringe	Adult	F	Type 2	None	None	No	A B C	Humulin N	Novolog	Lantus	Did not understand task
8	Insulin Experienced	Pen	Adult	F	Type 1	None	None	No	B A C	Humulin N	Apidra	Success	Did not understand task
16	Lantus SoloSTAR	Pen	Adolescent	M	Type 1	None	None	No	B A C	Success	Success	Lantus	Chose their pen
27	Insulin Experienced	Vial Syringe	Adult	M	Type 2	None	None	No	B A C	Humalog 600	Novolog	Lantus	Did not understand task
30	Insulin Experienced	Pen	Adult	M	Type 1	None	None	No	B A C	Success	Success	Lantus	Did not understand task
39	Primary Care Physician									Humulin N Carton	Humulin N Pen		Did not understand task
51	Lantus SoloSTAR	Pen	Elderly	F	Type 2	None	None	No	B A C	Success	Novolog	Success	Chose their pen
Updated instruction to have subject repeat task back to moderator to check understanding													
62	Nurse Practitioner									Humalog Carton	Success		Error – did not bring Rx to refrigerator
74	Insulin Experienced	Pen	Elderly	M	Type 1	None	None	Yes	B A C	Success	Apidra	Success	Looked like their pen
78	Insulin Experienced	Pen	Elderly	M	Type 2	Rheumatoid Arthritis	Multiple	No	B A C	Humalog 600	Success	Success	Error - Overlooked BIV pen

Note: Training occurred after the differentiation task, so effectively all people doing differentiation were untrained

8 Patient Errors:

The 8 patients (all insulin experienced) who chose the wrong pen in 1 or 3 of the scenarios stated that they did not understand the purpose of the differentiation task, chose their own

pen, or chose the pen that was appealing to them. Most of them selected the pens prior to receiving the task instructions.

2 HCP Errors:

The 2 HCPs was focused on the KwikPen, not the product name, did not bring the Rx to the refrigerator, or was focusing on the directions (“at bedtime”) and did not check the product name “Product X”.

B.2.2 Dial the Dose

Table 6-9 Demographics for Dial the Dose Errors

#	Trained/Untrained	Quota Segment	Pen, Vial/Syringe	Pen Name	Age	Gender	Type of Diabetes	Type of Hand Impairment	Type of Eye Impairment	Color blind	Error
3	Untrained	Insulin Naïve	n/a	n/a	Elderly	M	Type 2	Rheumatoid Arthritis	n/a	Yes	Dialed 2 unit prime
7	Untrained	Insulin Experienced	Pen	Multiple	Elderly	M	Type 1	n/a	n/a	Yes	Dialed 2 unit prime
8	Trained	Insulin Experienced	Vial Syringe	n/a	Elderly	M	Type 2	n/a	n/a	Yes	1 unit misdial

- 1 patient misdialed by 1 unit. When asked to dial the dose again, the patient correctly dialed 14 units.
- 2 patients dialed the 2 unit prime dose. 1 untrained patient was looking at the priming step in the IFU and forgot the assigned dose and felt nervous. The other untrained patient forgot to look at the prescription and indicated that he knew how to dial and stated that “you can take another 12 units; no problem.”

B.2.3 Deliver the Desired Dose

Table 6-10 Demographics for Deliver the Desired Dose Errors

#	Trained/Untrained	Quota Segment	Pen or Vial/Syringe	Age	Gender	Type of Diabetes	Type of Hand Impairment	Type of Eye Impairment	Color blind	Error
13	Untrained	Insulin Experienced	Vial/Syringe	Elderly	F	Type 2	None	Cataracts	No	Not returned to zero
22		Nurse Practitioner		Adult	F				No	Not returned to zero
35		Pharmacist		Adult	F				No	Not returned to zero
38		Endocrinologist		Adult	M				No	Inner needle shield not removed
62		Nurse Practitioner		Adult	F				No	Not returned to zero
75	Untrained	Insulin Naïve	n/a	Adult	M	Type 2	None	None	No	Inner needle shield not removed
77	Untrained	Insulin Experienced	Pen	Adult	F	Type 1	Multiple	Retinopathy	No	Inner needle shield not removed
82	Untrained	Insulin Naïve	n/a	Elderly	M	Type 2	Osteoarthritis	Cataracts	No	Not returned to zero

4 Patient Errors:

- 2 untrained patients did not press the button all the way in. 1 patient noticed that the dial did not return to zero. The other patient did a quick count to 5 but did not check the dose window.

- 2 untrained patients did not remove the inner needle shield.

4 HCP Errors:

- 3 HCPs did not press the button all the way down and stated that if it was for a real patient, they would make sure to check that the entire dose was injected.
- 1 HCP did not remove the inner needle shield.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Basaglar labels and labeling submitted by Lilly on October 17, 2013.

- Container label
- Carton labeling
- Instructions for Use
- Medication Guide

C.2 Label and Labeling Images



¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



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

/s/

SARAH K VEE
04/08/2014

YELENA L MASLOV
04/10/2014



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

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1790

Memorandum

Date: 3/18/2014

From: Faruk Sheikh, Ph.D., Laboratory of Immunology
Daniela Verthelyi, MD, Ph.D., Chief, Laboratory of Immunology

IND: NDA 205692, (Insulin Glargine, produced in E.coli)

Indication: Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus

Sponsor: Eli Lilly and Company

10-Month User Fee Goal Date: August 18, 2014

Recommendation: The review could not be completed due to insufficient information. An IR is communicated to the Sponsor.

Information requests (Immunogenicity):

Q1: Your data indicated that the number of patients with detectable insulin antibodies at week 52 in study ABEB was similar to LANTUS® (LY2963016: 40.4% to LANTUS®: 39.3%). However, in the 24 week ABEC study, at least 4% more subjects had anti-LY296301 antibodies than those treated with LANTUS® (Table ABEC 12.14). There is concern regarding the clinical impact of these antibodies. To help elucidate this question please provide the following information:

1. Samples that are positive for the presence of anti-drug antibody at least one time point during the course of the study, should be considered to be an anti-drug antibody (ADA) positive sample, regardless of the patient's ADA status at baseline. Confirm that overall number of ADA+ patient from both treatment group included patients who were ADA+ for at least one time-point of the study.
2. You are using antibodies raised against LY2963016 in your assays as reference standards. Provide data demonstrating that these antibodies bind with equal affinity to Lantus and LY2963016.
3. Provide the titer of the antibodies induced in ADA positive samples.

Q2: Provide data on the crossreactivity of the antibodies to LY2963016 with native insulin. Additionally, if you have data on the neutralizing capacity of these antibodies, please provide it for review.

Background:

Eli Lilly submitted this NDA (insulin glargine) for LY2963016 under section 505(b)(2) of FDA act. The 505(b)(2) application relies in part on the previous finding of safety and efficacy for a reference product approved by FDA. As per FDA draft guidance LY2963016 should show similarity to LANTUS® with respect to structure, function, animal toxicity, PK-PD, clinical immunogenicity, clinical safety and effectiveness.

LY2963016 uses LANTUS® (insulin glargine) produced by Sanofi-Aventis as the reference licensed product. (b) (4)

The safety profile and immunogenicity of LY2963016 in patients with T1DM and T2DM was evaluated by the sponsor in two Phase 3 studies (n=1291). LY2963016 (100U/mL) and LANTUS® (100U/mL) administered QD subcutaneously.

Phase 3 Studies			
ABEB	Comparison of LY2963016 with LANTUS® (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with premeal insulin lispro	Patients with T1DM (open-label)	536
			LY2963016: 269 LANTUS®: 267 (US-approved: 96/ EU-approved: 171)
ABEC	Comparison of LY2963016 with LANTUS® (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with OAMs	Patients with T2DM (double-blind)	759
			LY2963016: 379 LANTUS®: 380 (US-approved: 215/ EU-approved: 165)

A total of 1295 patients (4 patients did not complete) were randomized in Phase 3 studies (LY2963016: 648; LANTUS®: 647) and 60% of the patients enrolled in Study ABEC were insulin-naïve.

Important Note: The Sponsor has a validated (by the agency) binding assay for ADA to insulin glargine but does not have a neutralizing antibody assay.

Clinical-safety summary:

Treatment-Emergent Antibody Response (TEAR), Phase 3 studies:

Insulin-antibody positive at baseline: TEAR was defined as an absolute increase of at least 1% in insulin antibody levels and at least a 30% relative increase from baseline.

Negative for insulin antibodies at baseline: TEAR was defined as changing from insulin-antibody negative to antibody-positive during the course of the study following treatment with study drug.

ABEB Study (T1DM patients only):

**Table ABEB.12.15. Proportion of Patients with Detectable Antibodies
Summary and Analysis by Visit
Full Analysis Set
Study I4L-MC-ABEB: Overall Study (Treatment and Extension)**

Variable Analyzed: Proportion of Patients with Detectable Antibodies				
Visit (Week)	LY2963016 (N=268) n (%)	Lantus (N=267) n (%)	Total (N=535) n (%)	p-value* ^a
Baseline				
Number of Patients	265	267	532	
Patients with Detectable Antibodies	45 (17.0)	55 (20.6)	100 (18.8)	.318
Visit 4 (6)				
Number of Patients	262	262	524	
Patients with Detectable Antibodies	49 (18.7)	63 (24.0)	112 (21.4)	.166
Visit 5 (12)				
Number of Patients	257	262	519	
Patients with Detectable Antibodies	49 (19.1)	50 (19.1)	99 (19.1)	>.999
Visit 7 (24)				
Number of Patients	251	258	509	
Patients with Detectable Antibodies	48 (19.1)	45 (17.4)	93 (18.3)	.648
Visit 11 (52)				
Number of Patients	247	245	492	
Patients with Detectable Antibodies	70 (28.3)	54 (22.0)	124 (25.2)	.120
Abbreviations: LOCF = last observation carried forward; N = number of patients with detected or non-detected insulin antibody levels at baseline and post-baseline visits and treatment arm; n = number of patients in the specified category.				
Note: Only patients with detected or non-detected insulin antibody levels at baseline and post-baseline were included in analysis.				
*a - Treatment comparison was analyzed using the Fisher's Exact test or Pearson's Chi-square test. To avoid computational problems for p-value calculation, a maximum computation time = 5 minutes was programmed into the analysis for Fisher's Exact test. If it did not converge in this time, then Pearson's Chi-Square test was used. p-values shown on this column were from the Fisher's Exact test, unless they were obtained from the Pearson's Chi-Square test, which are shown with a suffix "§".				
Endpoint 52 Weeks (LOCF)				
Number of Patients	265	267	532	
Patients with Detectable Antibodies	73 (27.5)	59 (22.1)	132 (24.8)	.160
Overall 24 Weeks				
Number of Patients	265	267	532	
Patients with Detectable Antibodies	80 (30.2)	90 (33.7)	170 (32.0)	.404
Overall 52 Weeks				
Number of Patients	265	267	532	
Patients with Detectable Antibodies	107 (40.4)	105 (39.3)	212 (39.8)	.859

Reviewer's Comment: Patients (T1DM) with detectable insulin antibodies among all patients by visit, 52-week study, 107 patients (40.4%) had detectable antibodies to insulin (LY2963016) in compare to LANTUS® (105 patients, 39.3%). The overall difference may not be statistically significant but the above table indicated that more number of patients were ADA+ with LY2963016 than LANTUS at visit 11.

ABEC Study (T2DM patients only):

**Table ABEC.12.14. Proportion of Patients with Detectable Antibodies
Summary and Analysis by Visit
Full Analysis Set
I4L-MC-ABEC**

Variable Analyzed: Proportion of Patients with Detectable Antibodies

Visit (Week)	LY2963016 (N=376) n (%)	Lantus (N=380) n (%)	Total (N=756) n (%)	p-value* ^a
Baseline				
Number of Patients	365	365	730	
Patients with Detectable Antibodies	20 (5.5)	13 (3.6)	33 (4.5)	.285
Visit 6 (4)				
Number of Patients	362	359	721	
Patients with Detectable Antibodies	26 (7.2)	13 (3.6)	39 (5.4)	.047
Visit 10 (12)				
Number of Patients	351	344	695	
Patients with Detectable Antibodies	25 (7.1)	23 (6.7)	48 (6.9)	.882
Visit 16 (24)				
Number of Patients	337	328	665	
Patients with Detectable Antibodies	29 (8.6)	19 (5.8)	48 (7.2)	.179
Endpoint (LOCF)				
Number of Patients	365	365	730	
Patients with Detectable Antibodies	30 (8.2)	22 (6.0)	52 (7.1)	.314
Overall				
Number of Patients	365	365	730	
Patients with Detectable Antibodies	56 (15.3)	40 (11.0)	96 (13.2)	.100

Reviewer's Comment: In study I4L-MC-ABEC (T2DM), number of patients with detectable antibodies to LY2963016 as well as to LANTUS increased with visits until visit 16 (24-week). The table indicated that there were no significant overall differences in number of patient with detectable antibodies to LY2963016 and LANTUS, however when compared overall number of patients with antibodies to insulin, the patients treated with LY2963016 had at least 4% higher number of patients were ADA+ in compare to LANTUS (Table ABEC 12.14).

ABEB and ABEC together (T1DM and T2DM):

**Table 2.7.4.16. Proportion of Patients with Detectable Antibodies
Summary and Analysis by Visit
Full Analysis Set
LY2963016 ISS: I4L-MC-ABEB (52 Weeks), I4L-MC-ABEC (24 Weeks)**

Variable Analyzed: Proportion of Patients with Detectable Antibodies					
Visit (Week)	LY2963016 (N=644) n (%)	Lantus (N=647) n (%)	Total (N=1291) n (%)	p-value*a	p-value*b
Baseline					
Number of Patients	630	632	1262		
Patients with Detectable Antibodies	65 (10.3)	68 (10.8)	133 (10.5)	.805	.104
12 Weeks					
Number of Patients	608	606	1214		
Patients with Detectable Antibodies	74 (12.2)	73 (12.0)	147 (12.1)	.895	.853
24 Weeks					
Number of Patients	588	586	1174		
Patients with Detectable Antibodies	77 (13.1)	64 (10.9)	141 (12.0)	.215	.412
Endpoint					
Number of Patients	630	632	1262		
Patients with Detectable Antibodies	103 (16.3)	81 (12.8)	184 (14.6)	.064	.908
Overall					
Number of Patients	630	632	1262		
Patients with Detectable Antibodies	163 (25.9)	145 (22.9)	308 (24.4)	.196	.226

Abbreviations: LOCF = last observation carried forward; N = number of patients with detected or non-detected insulin antibody levels at baseline and post-baseline visits and treatment arm; n = number of patients in the specified category;

Reviewer's Comment: Patient with T1DM and T2DM together were compared after treatment with LY2963016 and LANTUS in the table above. Although both group of patients had similar ADA+ patients at baseline, at 24 weeks of the treatment at least 2% more patients were ADA+ with LY2963016 in compare to LANTUS indicating that LY2963016 may be more immunogenic than LANTUS. When considered overall ADA+ patients, the difference is 3.0% higher in patients treated with LY2963016 in compare to LANTUS.

T1DM and T2DM TEAR:

**Table 2.7.4.18. Treatment Emergent Antibody Response (TEAR)
Summary and Analysis by Visit, Endpoint (LOCF) and Overall
Full Analysis Set
LY2963016 ISS: I4L-MC-ABEB (52 Weeks), I4L-MC-ABEC (24 Weeks)**

Variable Analyzed: Treatment Emergent Antibody Response (TEAR)					
Visit (Week)	LY2963016 (N=630) n (%)	Lantus (N=632) n (%)	Total (N=1262) n (%)	p-value ^a	p-value ^b
12 Weeks					
Number of Patients	608	606	1214		
Patients with TEAR	48 (7.9)	36 (5.9)	84 (6.9)	.170	.191
24 Weeks					
Number of Patients	588	586	1174		
Patients with TEAR	52 (8.8)	37 (6.3)	89 (7.6)	.093	.476
Endpoint (LOCF)					
Number of Patients	630	632	1262		
Patients with TEAR	75 (11.9)	52 (8.2)	127 (10.1)	.027	.205
Overall					
Number of Patients	630	632	1262		
Patients with TEAR	127 (20.2)	103 (16.3)	230 (18.2)	.066	.839

Abbreviations: LOCF = last observation carried forward; N = number of patients with detected or non-detected insulin antibody levels at baseline and post-baseline visits and treatment arm; n = number of patients in the specified category; TEAR = treatment emergent antibody response.

^a - Frequencies analyzed by treatment using Cochran-Mantel-Haenszel (CMH) test stratified by study
^b - Homogeneity of odds ratios across studies was assessed using the Breslow-Day test.

Note1: Treatment Emergent Antibody Response (TEAR) is defined as an absolute increase of at least 1% in insulin antibody levels (measured in % binding) and at least 30% relative increase from baseline [for patients who are insulin antibody-positive at baseline] or turning from insulin antibody-negative status at baseline to antibody-positive during the course of the study following treatment with study drug.

Note2: Only patients with detected or non-detected insulin antibody levels at baseline and post-baseline were included in analysis.

Program Location: home/lillyce/prd/ly2963016/integrations/submission/programs_stat/smlaba6
Output Location: home/lillyce/prd/ly2963016/integrations/submission/programs_stat/tfl_output/smlaba61.rtf
Data Set Location: home/lillyce/prd/ly2963016/integrations/idb_q22013/data/ads

Reviewer's Comment: *The Sponsor analyzed overall immunogenicity data with respect to TEAR in the above table. The data indicated that there is a tendency to increase the number of patient to be ADA+ positive for the patients treated with LY2963016 over time at least by 4% point (Table 2.7.4.18). This difference may be considered significant with respect to TEAR and should be reported in the labeling information.*

Information requests (Immunogenicity):

Q1: Your data indicated that the number of patients with detectable insulin antibodies at week 52 in study ABEB was similar to LANTUS® (LY2963016: 40.4% to LANTUS®: 39.3%). However, in the 24 week ABEC study, at least 4% more subjects had anti-LY296301 antibodies than those treated with LANTUS® (Table ABEC 12.14). There is concern regarding the clinical impact of these antibodies. To help elucidate this question please provide the following information:

4. Samples that are positive for the presence of anti-drug antibody at least one time point during the course of the study, should be considered to be an anti-drug antibody (ADA) positive sample, regardless of the patient's ADA status at baseline. Confirm that overall number of ADA+ patient from both treatment group included patients who were ADA+ for at least one time-point of the study.
5. You are using antibodies raised against LY2963016 in your assays as reference standards. Provide data demonstrating that these antibodies bind with equal affinity to Lantus and LY2963016.
6. Provide the titer of the antibodies induced in ADA positive samples.

Q2: Provide data on the crossreactivity of the antibodies to LY2963016 with native insulin. Additionally, if you have data on the neutralizing capacity of these antibodies, please provide it for review.

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

/s/

FARUK G SHEIKH
04/03/2014

DANIELA I VERTHELYI
04/10/2014

MEMORANDUM

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

DATE: 03/18/2014

TO: Director, District Office
Baltimore District Office (BLT-DO)
6000 Metro Dr., Suite 101
Baltimore, MD 21215

Chief,
Medical Products & Tobacco Trip Planning Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER PDUFA, High Priority Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 205-692
DRUG: Insulin Glargine
SPONSOR: Eli Lilly and Company

This memo requests that you arrange for inspections of the clinical and analytical portions of the following Pharmacokinetic/Pharmacodynamic (PK/PD) and bioequivalence (BE) studies.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo to schedule the inspection of the analytical site. A DBGLPC scientist with specialized knowledge will participate in the inspection of analytical study site to provide scientific and technical expertise.

The inspections should be completed prior to 06/30/2014 to meet the PDUFA review due date.

Do not reveal the applicant, application number, studies to be inspected, drug name, or the study investigators to the sites

prior to the start of the inspections. The sites will receive this information during the inspection opening meeting. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.

Study #: I4L-MC-ABEO
Study Title: "Comparative Pharmacokinetics and Pharmacodynamics of LY2963016 and US-Approved LANTUS® after Single-Dose Subcutaneous Administration to Healthy Subjects"

Study #: I4L-MC-ABEN
Study Title: "Bioequivalence of US LANTUS® to EU LANTUS® after Single-Dose Subcutaneous Administration to Healthy Subjects"

Clinical Site: Lilly-NUS Centre for Clinical Pharmacology Pte. Ltd.; Level 6 Clinical Research Centre MD 11; National University of Singapore
10 Medical Drive, Singapore 117597
(Tel) +65-6413-9811
(Fax) +65-6779-0587

Investigator: Danny Soon, MD

SECTION A - RESERVE SAMPLES

Because **study I4L-MC-ABEO is a bioequivalence study**, this bioequivalence study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the Applicant for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>). Please note that **reserve samples are not required for study I4L-MC-ABEN.**

During the clinical site inspection, please:

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the DBGLPC POC immediately.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

During the clinical site inspection, please:

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.
- Compare the study report in the NDA submission to the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection:_____
 - o Number of subjects screened at the site:_____
 - o Number of subjects enrolled at the site:_____
 - o Number of subjects completing the study:_____
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

SECTION C - AUDIT OF ANALYTICAL DATA

Analytical Site:

_____ (b) (4)

(b) (4)

Contact person:

(b) (4)

Methodology:

Radioimmunoassay (RIA)

During the analytical site inspection, please:

- Examine all pertinent items related to the analytical methods used for the measurement of analyte concentrations in human serum.
- Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- Determine if the site employed validated analytical methods to analyze the subject samples.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.
- Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.
- Examine correspondence files between the analytical site and the applicant for their content.

Additional instructions to the ORA Investigator:

Please follow up on corrections in response to the Untitled Letter issued to the analytical site [REDACTED] (b) (4) [REDACTED].

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the DBGLPC POC.

DBGLPC POC: Arindam Dasgupta, Ph.D.
Pharmacologist
Office of Scientific Investigations
Tel: 1-301-796-3326
Fax: 1-301-847-8748
E-mail: arindam.dasgupta@fda.hhs.gov

DARRTS cc:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Bonapace/Haidar/Skelly/Choi/Dasgupta/Dejernett

OSI/DBGLPC/Bonapace/Mada

OMPT/CDER/OND/ODEII/DMEP/Callie Cappel-Lynch/Parks

Email cc:

ORAHQ/OMPTO/DMPTI/BIMO/Turner/Arline/Montemurro/Colon/Carrion

OMPT/CDER/OND/ODEII/DMEP/Callie Cappel-Lynch/Parks

ORA/CE-FO/BLT-DO/Evelyn Bonnin/Harris

Draft: AD 3/13/2014

Edit: MFS 3/13/2014

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

Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ Lilly-NUS Centre for Clinical Pharmacology, Singapore

OSI file #: (b) (4)

FACTS: (b) (4)

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

/s/

ARINDAM DASGUPTA
03/18/2014

SAM H HAIDAR
03/18/2014

Date: March 13, 2014
From: Lening Shen, WO66, RM 2558
General Hospital Devices Branch, DAGRID, ODE, CDRH

To: Callie Cappel-Lynch, DMEP/CDER
Subject: CDRH Consult, ICC1300540, NDA 205692, Eli Lilly and Company
LY2963016 KwikPen™ (LY2963016 KP)

Consultants: Patricia Beaston, MD, Ph.D, CDRH/ODE/DAGRID
Rakhi Dalal, Ph.D., CDRH/ODE/DAGRID
R. Kapil Panguluri, Ph.D., CDRH/ODE/DAGRID

1. Issue

This consult is to determine if the sponsor has provided adequate device related information for CDRH to conduct a 510(k) clearance type of performance (Sterility, Biocompatibility and Bench) review on the device of the submission.

2. Documents Reviewed

Section 3.2.R.3 (medical-device.pdf)

Additional information provided based on inquiry of original consult review. Email received on December 17, 2014.

The sponsor provided the following description of the device.

The information in Section 3.2.P.7 includes the description and controls for the LY2963016 drug product multi-dose cartridge container closure system.

The drug product is filled into a Type 1 glass cartridge. The cartridge is sealed with a (b) (4) disc seal and with a gray (b) (4) plunger. The following table provides the descriptions for the primary packaging components.

Table 3.2.P.7.2-1 Package Size and Description for Container Closure System

Drug Product Strength (U/mL)	Cartridge Size	Packaging Components and Identification
100	3 mL	<u>Primary Components</u> Cartridge: Type I clear glass. Disc Seal: (b) (4) (b) (4) Plunger: (b) (4)



The sponsor referred to the following standards:

Table 3.2.P.7.4-1 Compendial References for Primary Packaging Components

Packaging Component	Relevant Standard
Cartridge	The glass cartridges comply with applicable limits for Type 1 glass in USP <660>, Containers – Glass.
Disc Seal	The elastomeric disc complies with requirements for Type 1 elastomeric closures in USP<381>, Elastomeric Closures for Injections.
Plunger	The elastomeric plunger complies with requirements for Type 1 elastomeric closures in USP<381>, Elastomeric Closures for Injections.

3. CDRH Review and Comments

The sponsor has provided Sterility, Biocompatibility, and Bench performance test reports.

Clinical

Dr. Patricia Beaston reviewed the summary data and concluded that the sponsor has submitted adequate information for her to conduct a clinical review of the device component. The Sponsor is proposing an insulin glargine 505(b)(2) under the trade name (b) (4). The dose accuracy performance meets requirements. She believes that no new clinical issues were identified for the device component of this combination product.

Sterility

R. Kapil Panguluri, Ph.D. of INCB reviewed the sterility information provided by the sponsor. The sponsor stated that the LY2963016 KwikPen is not a sterile device; therefore there is no sterility report. The device components of the KwikPen do not need to be sterilized because the components of the pen-injector do not contact the drug product. The drug product is contained in its primary container closure (cartridge) and the fluid path into the body is through an attached, disposable, single-use sterile needle. The needle is not supplied by Lilly; it is purchased separately by the user. There are no concerns about interaction between the drug product and the device components because there is no contact between these components.

Based on the information provided, the drug is enclosed in a cartridge and the material of which has not been changed in this present sub. The only portion that was changed is the plunger which does not come in contact with the patient or the drug. Hence, R. Kapil Panguluri, Ph.D. of INCB agrees with the firm's response that the sterility is not required as the change in plunger material does not contact the drug cartridge.

Biocompatibility

The sponsor stated that a biological evaluation was performed on the KwikPen platform of devices in accordance with ISO 10993-1:2009. This evaluation included the currently marketed version of KwikPen and versions under evaluation by regulatory agencies. The LY2963016 device is included in the scope of this evaluation as documented in PDS-

REPORTS-01696 *Biological Evaluation of KwikPen Device Platform*. Section 7 of the report concluded that:

“KwikPen is classified as a limited duration skin contact device. Users of the device hold it in their hands for a minute or two a few times per day. The risk to the user is low based on the limited contact. The plastic materials used in the device are well understood by their manufacturers and have been used for several years by Lilly. The analysis referred to in this report has been reviewed by Lilly corporate toxicologist who has confirmed that the plastic materials used in the KwikPen platform have been evaluated according to the guidance in ISO 10993-1 and pose no additional risk to patient safety.”

Rakhi Dalal, Ph. D. of GHDB reviewed the information submitted by the sponsor and believed that they are deficient. It appears that there are several configurations of Kwik Pen. Also, there may be other modification eliciting Human factor review of the dose-color identification. In regards to biocompatibility, in the submission only biocompatibility of Kwik Pen material of construction for the LY2963016 cartridge holder is provided. As FDA clears/approves medical devices and biocompatibility assessments are used for analyzing post manufacturing residuals and not the raw materials used in construction, she listed two deficiencies regarding found in this submission below.

Bench

The sponsor stated that the design verification testing in accordance with ISO11608-1:2012 was performed using preapproved protocol PDS-PROTOCOLS-00336 *KwikPen* (b) (4) *ISO11608-1 Design Verification Test Protocol*. The results of the ISO11608 testing along with Lilly specific testing are included in PDS-REPORTS-01164 (b) (4) *Design Verification Technical Report*. Section 10 of the report concluded that:

“The (b) (4) Design Verification Builds, PDS Lots #12220-001 and 12299-001 met all design verification acceptance criteria for ISO11608-1:2012, per PDS-PROTOCOLS-00336. The design also meets design verification acceptance criteria for Lot Release Dose Accuracy per PDS-00011-LOCAL-NC and Functional Attributes Testing per PDS-PROTOCOLS-00252.

Therefore, the design output for the KwikPen (b) (4) device meets the design input requirements tested.”

The protocol and technical report are provided in the response to our questions. The sponsor indicated that all tests pass.

However, for the glass cylinder, the sponsor has not provided performance testing information, such as for the cylinder or the plunger. We recommend that the sponsor provide this information based on ISO 13926-1 and -2.

4. CDRH Recommendation

CDRH/ODE recommends the following deficiencies to be relayed to the NDA sponsor:

1. In NDA 205692 you have indicated that the LY2963016 will be made available in a 3 mL cartridge sealed in a prefilled pen injector (KwikPen™). The submission indicates that changes with regards to pen injector was made, i.e., the plunger component which can impact the patient safety. Please provide the side-by-side comparison of the previous KwikPen device and the new and modified KwikPen in terms of design, patient/drug contacting device components, materials used in manufacturing including (b) (4) of the new prefilled pen injector (KwikPen™). Information in regards to the device is limited.
2. Page 44/171 states “KwikPen is classified as a limited duration skin contact device. ... plastic materials used in the KwikPen platform have been evaluated according to the guidance in ISO 10993-1”. As FDA clears or approves medical devices and biocompatibility assessments in medical device applications are considered for evaluating post-manufacturing residuals in the final finished device, limitations apply when utilizing raw material biocompatibility for medical product clearance or approval. Based on the identified classification, please provide complete biocompatibility study reports for FDA evaluation. If you have leveraged the biocompatibility studies based on existing predicate device or have submitted the reports elsewhere in the submission, you may provide the information for evaluation.
3. In your submission, we cannot locate performance testing information on your glass cylinder and the enclosed plunger. We recommend that you follow ISO 13926-1 and ISO 13926-2 when conducting your performance testing. Please provide us your reports including test protocol, test data, pass/fail criteria, and test results.

Digital Signature Concurrence Table	
Reviewer Sign-Off	 Digitally signed by Lening Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lening Shen -S, 0.9.2342.19200300.100.1.1=1300435455 Date: 2014.03.13 15:34:12 -04'00'
Branch Chief Sign-Off	 Digitally signed by Richard C. Chapman Date: 2014.03.14 11:03:48 -04'00'

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/s/

CALLIE C CAPPEL-LYNCH
03/14/2014
signing for Lening Shen CDRH



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

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1790

Amendment

Date: 02/07/2014
From: Faruk Sheikh, Ph.D., Laboratory of Immunology
Kirshner Susan, Chief, Regulatory Affairs, Division of Therapeutic Proteins
Daniela Verthelyi, MD, Ph.D., Chief, Laboratory of Immunology
NDA: 205692
Subject: Amendment to Immunogenicity assay review
Product: (b) (4) KwikPen, (recombinant insulin glargine for injection).
Indication: SC administration in patients for the control of (b) (4)
Sponsor: Eli Lilly and Co

Recommendation: The validation of the anti-LY2963016 antibodies is complete.

Review Summary: In response to IR, the Sponsor stated that the cut-point using serum samples from patients with diabetes were higher than that obtained from normal donors. This is because many patients may have pre-existing anti-insulin antibodies. Nevertheless, the Sponsor decided to use the cut-point obtained from normal donors in order to minimize the risk of missing any true positive. The Agency concurs with the Sponsor's decision. Therefore, the validation of the assay is complete.

An IR with the following comment was e-mailed to the Sponsor on Wednesday, February 05, 2014. Sponsor's response to the IR request is as follows:

Agency's comment: *The cut point for the screening assay should be established using sera from treatment naïve patients whenever possible. Confirm the cut point for the anti-insulin glargine antibody screening assay using sera from treatment naïve type1 and type2 diabetes mellitus patients.*

Sponsor's Response: The cut-point for the LY2963016 immunogenicity assay was actually established using samples obtained from normal donors and these data are contained in the validation package. Note that these normal donor samples were from healthy volunteers without diabetes and were not enrolled in any Lilly studies. We also looked at baseline (pre-treatment) samples from patients with diabetes in the phase 3 studies and determined what the cut-point would have been using these disease state samples (and applying a 5% threshold limit consistent with FDA guidance). Not surprisingly, the cut-point using the disease state samples was higher than that obtained

from normal donors since many patients will have been treated with exogenous insulin for years and already formed anti-insulin antibodies. In light of this, we elected to go with the more conservative cut point obtained from the normal donors in order to minimize the risk of missing any true positives.

From: Joerg Pfeifer [mailto:pfeifer_joerg@lilly.com]
Sent: Friday, February 07, 2014 7:35 AM
To: CappelLynch, Callie
Cc: Joerg Pfeifer
Subject: RE: NDA 205692 Information Request - cut point for screening assay

Hi Callie,

Please find below our response to your question on the cut point for the screening assay. I wanted to get it to you quickly and thus am responding by email. Can you please confirm my assumption that I need to formally provide this as a response to the NDA as well? Thank you, Joerg

The cut-point for the LY2963016 immunogenicity assay was actually established using samples obtained from normal donors and these data are contained in the validation package. Note that these normal donor samples were from healthy volunteers without diabetes and were not enrolled in any Lilly studies. We also looked at baseline (pre-treatment) samples from patients with diabetes in the phase 3 studies and determined what the cut-point would have been using these disease state samples (and applying a 5% threshold limit consistent with FDA guidance). Not surprisingly, the cut-point using the disease state samples was higher than that obtained from normal donors since many patients will have been treated with exogenous insulin for years and already formed anti-insulin antibodies. In light of this, we elected to go with the more conservative cut point obtained from the normal donors in order to minimize the risk of missing any true positives.

Joerg Pfeifer PhD
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From: CappelLynch, Callie [mailto:Callie.Cancell_ynch@fda.hhs.gov]
Sent: Wednesday, February 05, 2014 9:39 AM
To: Joerg Pfeifer
Subject: NDA 205692 Information Request

Hi Joerg,

We have one additional request for information for NDA 205692.

The cut point for the screening assay should be established using sera from treatment naïve patients whenever possible. Confirm the cut point for the antiinsulin glargine antibody screening assay was established using sera from treatment naïve type1 and type2 diabetes mellitus patients.

Please respond to this request within 4 weeks. If you are unable to do so, please provide me with an estimated time to expect your response.

Thank you,
Callie

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

/s/

FARUK G SHEIKH
02/28/2014

SUSAN L KIRSHNER
02/28/2014



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

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1790

Memorandum

Date: 11/07/2013

From: Faruk Sheikh, Ph.D., Laboratory of Immunology
Daniela Verthelyi, MD, Ph.D., Chief, Laboratory of Immunology

IND: NDA 205692

Subject: Immunogenicity assay review (consult) for DMEP

Product: (b) (4) KwikPen, (recombinant insulin glargine for injection).

Indication: SC administration in patients for the control of (b) (4)

Dose: 100 IU/mL, once a day.

Sponsor: ELI LILLY AND CO

Filing Meeting: December 4, 2013

Other Interim Meetings: TBD

EDR Location: \\CDSESUB1\evsprod\NDA205692\205692.enx

Recommendation: The validation of the anti-LY2963016 antibodies is complete with the following suggestion.

Comment to Sponsor: The cut point for the screening assay should be established using sera from treatment naïve patients whenever possible. Confirm the cut point for the anti-insulin glargine antibody screening assay using sera from treatment naïve type 1 and type 2 diabetes mellitus patients.

Review summary: The Sponsor submitted data supporting the validation of a Radio Immuno Assay (RIA) method for the detection and confirmation of anti-LY2963016 antibodies in human serum treated with LY2963016. The screening cut-point for anti-LY2963016 antibody was determined from 51 normal human serum to be 5.3%BT (Bound over Total Counts per Minute) and the assay specific confirmatory cut point in presence of excess drug was determined to be 0.26 %B/T. The Sponsor also determined a cut-point for insulin specific cross-reactivity which is 1.06 %B/T. The sensitivity of the binding assay was determined to be 25ng/mL using *affinity purified* polyclonal anti-human insulin antibody raised in guinea pig. Using 500 ng/mL of *affinity purified*

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polyclonal antibody this assay can tolerate insulin or LY2963016 concentrations up to 500ng/mL or 1000ng/mL respectively without decreasing the signal below the assay screening threshold of 5.30 %B/T. The antibodies against LY2963016 are stable during storage, processing, and analysis in human serum samples.

Product background:

LY2963016 is an *E. coli*-derived human insulin analog, manufactured using recombinant DNA technology. The molecule consists of 53 amino acids in two chains, 'A chain' (21 amino acids) and 'B chain' (32 amino acids) that are connected by disulfide linkages (two inter-chain and single intra-chain), like human insulin. The Sponsor stated LY2963016 is a long-acting blood-glucose lowering agent, remains active up to 24 hours.

A Chain: GIVEQCCTSI CSLYQLENYC G

B Chain: FVNQHLCSGH LVEALYL VCG ERGFFYTPKT RR

The differences in the amino acid sequence between human insulin and the product are:

1. Replacement of the C-terminal Asparagine of the A chain by **Glycine**.
2. Elongation of the C-terminal of the B chain by **two Arginine** residues.

The drug product, LY2963016 is intended to supply in a 3-mL glass cartridge with elastomeric disc seal and plunger for administration via SC injection. Each mL contains 100U LY2963016; glycerin (USP-NF), 17 mg; metacresol (USP-NF), 2.7 mg; zinc oxide (USP-NF) (b)(4) and water for injection (USP-NF). One mg of pure LY2963016 is equivalent to (b)(4) U of LY2963016. The cartridge will be assembled into a modified version of the currently marketed KwikPen.

Anti- LY2963016 antibody Screening Assay:

1. Analyte:

- Affinity Purified Guinea Pig anti-Human Insulin Polyclonal Antibody
- Guinea Pig anti-Human Insulin Polyclonal Antisera

The Sponsor stated that the Sensitivity and the Drug Tolerance samples used in validation exercise were prepared by adding affinity purified polyclonal anti-insulin antibodies to serum from normal healthy human adults.

2. **Matrix:** human serum

3. **Minimum Required Dilution (MRD):** 1:5.

4. **Detection Reagent:** ^[125]I-LY2963016.

5. Quality Controls: The Sponsor stated that the validation samples were prepared by spiking guinea pig polyclonal anti-insulin hyper-immune serum into pooled normal human serum at dilutions of 1:32,000, 1:5,500, and 1:2,000 to prepare low, mid and high positive controls respectively.

6. Negative Controls: Normal human serum pool.

7. Assay method:

An RIA method has been used for the detection and confirmation of anti-LY2963016 antibodies in human serum.

In this assay, 5% charcoal slurry was added (250uL) to the controls and the samples (500uL), followed by an addition of extraction acid (625uL of 0.12N HCl), and allowed to incubate for 10 minutes. The acid treated samples were neutralized with an addition of extraction base (625uL of 0.048N NaOH/0.06 M Tris) and spun down the charcoal.

For assay setup, 100uL of extracted sample was added to a glass tube followed by the addition of 100uL of assay buffer (0.05M Phosphosaline, pH 6.5, containing 0.025M EDTA, 0.08% Sodium Azide, and 1% BSA) and /or excess LY2963016 or excess insulin and incubated 1.5-2.5 hours at 37°C. Then 100uL of tracer (¹²⁵I-LY2963016) was added and incubated for 16-24 hours at 2-8°C temperature.

The samples were then precipitated with the addition of 200uL of ice cold 0.54% BGG (Bovine Gamma Globulin) and 500uL of ice cold 25% PEG (Polyethylene Glycol) and mixed and then the samples were incubated for 10-20 minutes at 2-8°C.

The samples were spun down for 35-40 minutes at 2-8°C and the supernatant were decanted and the pellets were washed with 2 ml of ice cold 12.5% PEG. The dry pellets were counted in a gamma counter.

8. Cut Point Determination:

The Sponsor provided data derived from 51 (healthy) individual human serum samples that were used to calculate the assay specific positive reactivity cut points. The Sponsor stated that the assay was performed in 3 runs in duplicate by two analysts over two days.

The antibody positive samples were competed in a Tier 2 fashion with either (1) excess cold LY2963016 or (2) insulin and the assay specific cut point was generated for each of the inhibitors used in Tier 2 screening. These values were used to discriminate between positive and negative anti-drug results as well as to discriminate between antibodies which are insulin cross-reactive or non-cross-reactive. The results were expressed as percent bound over total counts per minute (% BT) and was determined according to the following equation. Part of the data is presented in Fig4 (copied from the original).

$$\%B/T = [(Total\ Counts\ in\ Tier2 - NSB\ Counts) / Total\ Counts\ in\ Tier2] * 100.$$

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The cut points determined: **5.30% B/T** for positive reactivity Cut-Point
0.26 % B/T for LY2963016 (specificity cut-point) and
1.06 %B/T for cross reactivity to insulin.

Table 4 Screening Sensitivity and Drug Tolerance Threshold and Assay Specific Positivity Cut Point

Lot Number	Assay Number	Mean Response %B/T	Mean Response %B/T Total LY2963016	Mean Response %B/T Cross-reactive to insulin
BRH284200	201101061602.008	3.85	0.00	1.02
BRH284201	201101061602.008	2.97	0.00	0.07
BRH284202	201101061602.008	3.74	0.00	0.64
BRH284203	201101061602.008	3.82	0.00	0.62
BRH284204	201101061602.008	2.79	0.00	0.61
BRH284205	201101061602.008	3.88	0.00	0.60
BRH284206	201101061602.008	3.61	0.00	0.43
BRH284207	201101061602.008	2.45	0.00	¹ 0.00
BRH284208	201101061602.008	3.89	0.00	0.41
BRH284209	201101061602.008	2.85	0.00	0.36
BRH284210	201101061602.008	4.37	0.00	0.00
BRH284211	201101061602.008	3.78	0.00	0.38
BRH284212	201101061602.008	3.36	0.00	0.30
BRH284213	201101061602.008	3.89	0.00	0.61
BRH284214	201101061602.008	4.13	0.00	0.00
BRH284215	201101061602.008	5.29	0.01	0.97
BRH284216	201101061602.008	3.25	0.00	0.54
BRH284217	201101061602.008	5.15	0.10	² 0.00
BRH284218	201101061602.008	4.27	0.00	0.96
BRH284219	201101061602.008	4.36	0.00	0.25
BRH284220	201101061602.008	3.49	0.00	0.44
BRH284221	201101061602.008	3.42	0.00	0.70
BRH284222	201101061602.008	3.85	0.00	0.16
BRH284223	201101061602.008	4.59	0.27	0.83
BRH284224	201101061602.008	3.90	0.00	0.72
BRH284225	201101061602.008	4.99	0.46	1.34
BRH284226	201101061602.008	4.37	0.00	0.57
BRH284227	201101061602.008	4.27	0.08	0.66
BRH284228	201101061602.008	4.14	0.00	0.13
BRH284229	201101061602.008	3.93	0.00	0.51
BRH284230	201101061602.008	3.85	³ 0.00	0.00
BRH284231	201101061602.008	4.52	0.00	1.00
BRH284232	201101061602.008	4.10	0.00	0.63
BRH284233	201101061602.008	5.77	0.44	1.53
BRH284234	201101061602.008	4.56	0.00	0.60
BRH284235	201101061602.008	3.57	0.00	0.36
BRH284236	201101061602.008	4.41	0.13	0.66
BRH284237	201101061602.008	3.53	0.00	0.00
BRH284238	201101061602.008	4.35	0.00	0.00
BRH284239	201101061602.008	4.13	0.00	0.14

Run: 1, Analyst: 1

^{1,2} %CV of replicate results > 25%. Result not included in screening sensitivity and drug tolerance threshold and assay specific positivity cut point calculations.

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Table 4 Screening Sensitivity and Drug Tolerance Threshold and Assay Specific Positivity Cut Point (continued)

	Lot Number	Assay Number	Mean Response %B/T	Mean Response %B/T Total LY2963016	Mean Response %B/T Cross-reactive to Insulin
Run 2, Analyst 2	BRH284216	201101061917.008	2.89	0.00	0.76
	BRH284217	201101061917.008	3.11	0.00	0.45
	BRH284218	201101061917.008	3.08	0.00	0.03
	BRH284219	201101061917.008	2.92	0.00	0.27
	BRH284220	201101061917.008	2.79	0.00	0.50
	BRH284221	201101061917.008	^(a) 5.56	^(b) 0.55	^(b) 2.75
	BRH284222	201101061917.008	3.79	0.00	0.51
	BRH284223	201101061917.008	3.42	0.00	0.67
	BRH284224	201101061917.008	2.61	^(a) 2.38	0.00
	BRH284225	201101061917.008	3.90	0.00	0.71
	BRH284226	201101061917.008	3.94	0.00	0.00
	BRH284227	201101061917.008	3.94	0.00	^(d) NR
	BRH284228	201101061917.008	^(a) NR	^(b) NR	^(e) _
	BRH284229	201101061917.008	3.72	0.00	0.06
	BRH284230	201101061917.008	3.05	0.00	0.48
	BRH284231	201101061917.008	3.13	0.00	0.00
	BRH284232	201101061917.008	4.06	0.00	0.72
BRH284233	201101061917.008	5.13	0.00	0.41	

Run 3, Analyst 2	BRH284200	201101071831.008	^(a) 6.92	^(b) 2.21	^(b) 2.62
	BRH284201	201101071831.008	4.21	0.00	0.39
	BRH284202	201101071831.008	4.20	0.00	0.34
	BRH284203	201101071831.008	4.50	0.00	0.27
	BRH284204	201101071831.008	3.39	0.00	0.20
	BRH284205	201101071831.008	3.72	0.00	0.22
	BRH284206	201101071831.008	3.67	0.00	0.16
	BRH284207	201101071831.008	2.84	0.00	0.00
	BRH284208	201101071831.008	4.20	0.00	0.00
	BRH284209	201101071831.008	3.17	0.00	0.00
	BRH284210	201101071831.008	4.70	0.00	0.32
	BRH284211	201101071831.008	4.17	0.00	0.72
	BRH284212	201101071831.008	3.87	0.00	0.11
	BRH284213	201101071831.008	4.11	0.00	0.32
	BRH284214	201101071831.008	4.28	0.00	^(a) 0.00
	BRH284215	201101071831.008	4.16	0.00	0.33
	BRH284216	201101071831.008	^(a) 5.95	^(b) 0.00	^(b) 2.49
BRH284217	201101071831.008	4.23	0.00	0.29	
BRH284218	201101071831.008	4.19	0.00	0.00	
BRH284219	201101071831.008	4.91	0.00	0.71	

^(a) %CV of replicate results > 25%. Result not included in screening sensitivity and drug tolerance threshold and assay specific positivity cut point calculations.

^(b) Data calculated from sample with a %CV > 25%. Result not included in screening sensitivity and drug tolerance threshold and assay specific positivity cut point calculations.

^(c) No result. Processing error during assay.

^(d) Result cannot be calculated.

Mean	3.95	0.03	0.42
Std Dev	0.82	0.14	0.39
Factor	1.645	1.645	1.645
Cut Point	5.30	0.26	1.06

The Sponsor stated the cut point was calculated using the formula: Mean + (Std Dev * 1.645), according to Mire-Sluis et. al.¹ (2004) after removal of all values that had a high %CV or a processing error.

Calculation of Specificity Cut-point

Step 1: For specificity cut-point, the Tier 2 %B/T value was subtracted from the Tier 1 %B/T value for each data point.

¹ Mire-Sluis et. al. (2004): Recommendations for the design and optimization of immunoassays used in the detection of host antibodies against biotechnology products. Journal of Immuno Methods 289, 1 – 16.

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Step 2: The mean and standard deviation (SD) on Tier 2 minus Tier 1 % B/T data were calculated for each condition.

Result: Assay Cut-point negative mean = 3.95%B/T, SD = 0.82%B/T

Result: LY2963016 mean = 0.03%B/T, SD = 0.14%B/T

Result: Insulin mean = 0.42%B/T, SD = 0.39%B/T

Step 3: The SD was multiplied by 1.645 (95th percentile) for each condition.

Result: 95th percentile = 1.35%B/T

Result: LY2963016 95th percentile = 0.23%B/T

Result: Insulin 95th percentile = 0.64%B/T

Step 4: Cut-point = Mean + (1.645 * SD) from Step3.

Result: Positive Reactivity Cut-Point = (3.95+1.35) = **5.30%B/T**

Result: LY2963016 Specific Positive Reactivity Cut-Point = **0.26%B/T**

Result: Insulin Specific Positive Reactivity Cut-Point = **1.06%B/T**

OUTLIER IDENTIFICATION

The Sponsor calculated the outlier by adding four times of SD to the mean of the data.

Outlier criteria calculation:

Mean = 3.95%B/T, standard deviation = 0.82%B/T

Outlier criteria result: 7.23%B/T

Any outlier points (> 7.23%B/T) from the data set were identified as outliers.

Reviewer's Comment: The Sponsor established the cut-point for the binding assay followed by a confirmatory assay according to the equation recommended by Mire-Sluis et al., 2004, which is universally used by the industry in immunoassay development.

Radio Immuno assay (RIA) is very sensitive, specific, in vitro immunoassay technique. This is a popular platform for the assay development because of its robustness and consistent results. This approach to establish the cut-point is acceptable.

9. Validation parameters:

9.1 Precision:

9.1.1 Precision of Total Adjusted %B/T Response for Validation Samples:

The Sponsor stated that 6 runs were processed for the assessment of intra- and inter-assay precision, with three determinations for each run of the three positive controls (Low, Mid and High) and negative control concentrations (n=18). Validation samples were prepared

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by spiking guinea pig polyclonal anti-insulin hyper-immune serum into pooled normal human serum. The precision data are shown in Table 5.

Table 5 Precision of Total Adjusted %B/T Response for Validation Samples

	Assay Date	Analyst	Assay ID	%B/T				Intra-assay (within-run) Statistics			
				1st	2nd	3rd	4th	n	Mean	Std Dev	%CV
				Front	Front Mid	Back Mid	Back				
Negative	04-Jan-11	1	201101061602.008	3.40	4.04	2.73	4.49	4	3.67	0.77	20.9
	05-Jan-11	1	201101062334.008	1.87	4.24	1.62	3.60	4	2.83	1.29	45.4
	07-Jan-11	1	201101082013.008	4.29	6.63	4.77	4.64	4	5.08	1.05	20.7
	04-Jan-11	2	201101060157.008	3.47	2.15	3.08	3.81	4	3.13	0.72	22.9
	05-Jan-11	2	201101061917.008	3.64	3.68	3.64	3.87	4	3.71	0.11	3.0
	06-Jan-11	2	201101071831.008	4.02	5.21	6.21	5.09	4	5.13	0.90	17.5
	Intra-assay (within-run) statistics (Pooled):								4.00	3.92	0.88
Inter-assay (between-run) statistics (ANOVA):								24	3.92	1.24	31.5
Low (132,000)	04-Jan-11	1	201101061602.008	6.89	7.65	7.33	7.40	4	7.32	0.32	4.3
	05-Jan-11	1	201101062334.008	6.88	7.19	6.84	7.15	4	7.02	0.18	2.6
	07-Jan-11	1	201101082013.008	7.50	8.10	7.70	8.05	4	7.84	0.29	3.7
	04-Jan-11	2	201101060157.008	6.50	6.36	6.56	6.76	4	6.55	0.17	2.5
	05-Jan-11	2	201101061917.008	7.42	7.55	6.87	6.79	4	7.16	0.38	5.4
	06-Jan-11	2	201101071831.008	6.71	7.29	7.30	7.45	4	7.19	0.33	4.5
	Intra-assay (within-run) statistics (Pooled):								4.00	7.16	0.29
Inter-assay (between-run) statistics (ANOVA):								24	7.16	0.49	6.8
Mid (15,500)	04-Jan-11	1	201101061602.008	24.56	25.08	23.75	16.05	4	22.36	4.24	19.0
	05-Jan-11	1	201101062334.008	24.27	24.49	24.29	24.40	4	24.36	0.10	0.4
	07-Jan-11	1	201101082013.008	24.09	24.99	24.57	26.24	4	24.97	0.82	3.7
	04-Jan-11	2	201101060157.008	23.21	22.91	23.87	23.03	4	23.25	0.43	1.9
	05-Jan-11	2	201101061917.008	25.03	25.77	25.26	26.02	4	25.53	0.45	1.8
	06-Jan-11	2	201101071831.008	22.65	16.77	21.50	22.41	4	20.83	2.75	13.2
	Intra-assay (within-run) statistics (Pooled):								4.00	23.55	2.11
Inter-assay (between-run) statistics (ANOVA):								24	23.55	2.54	10.8
High (12,000)	04-Jan-11	1	201101061602.008	54.19	52.79	53.11	50.87	4	52.74	1.38	2.6
	05-Jan-11	1	201101062334.008	53.50	52.29	53.22	53.45	4	53.12	0.56	1.1
	07-Jan-11	1	201101082013.008	50.21	51.36	50.04	43.41	4	48.76	3.61	7.4
	04-Jan-11	2	201101060157.008	53.12	52.58	52.61	53.20	4	52.93	0.29	0.5
	05-Jan-11	2	201101061917.008	55.83	54.37	54.00	55.56	4	54.94	0.89	1.6
	06-Jan-11	2	201101071831.008	47.81	45.76	44.21	46.34	4	46.03	1.49	3.2
	Intra-assay (within-run) statistics (Pooled):								4.00	51.42	1.75
Inter-assay (between-run) statistics (ANOVA):								24	51.42	3.66	7.1

Reviewer's comment: The responses for all positive samples were proportionately increased from NC to high controls as expected with variability ranging from 3.4 to 9.0 %CV for intra-assay and from 6.8 to 10.8 %CV for inter-assay statistics. For negative samples, all but 2 of the 24 analyzed samples were above the calculated screening cut-point of 5.30 %B/T, which may be possible for a negative control because of the high sensitivity of the assay. Therefore, the intra- and inter assay precision is acceptable.

9.1.2 Precision of Total LY2963016 Response for Validation Samples:

The Sponsor stated that 6 runs were processed for the assessment of intra- and inter-assay precision, with three determinations for each run of the three positive controls (Low, Mid and High) and negative control concentrations (n=18). Validation samples were prepared by spiking guinea pig polyclonal anti-insulin hyper-immune serum into pooled normal human serum. The precision data are shown in Table 6.

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Table 6 Precision of Total LY2963016 Response for Validation Samples

	Assay Date	Analyst	Assay ID	%B/T				Intra-assay (within-run) Statistics			
				1st	2nd	3rd	4th	n	Mean	Std Dev	%CV
				Front	Front Mid	Back Mid	Back				
Negative	04-Jan-11	1	201101061602.008	0.00	0.03	0.00	0.12	4	0.03	0.06	200.0
	05-Jan-11	1	201101062334.008	0.00	0.00	0.00	0.00	4	0.00	0.00	^(b) —
	07-Jan-11	1	201101082013.008	0.00	0.51	0.00	0.00	4	0.13	0.26	200.0
	04-Jan-11	2	201101060157.008	0.00	0.00	0.00	0.14	4	0.04	0.07	200.0
	05-Jan-11	2	201101061917.008	0.00	0.00	0.00	0.00	4	0.00	0.00	^(b) —
	08-Jan-11	2	201101071831.008	0.00	0.56	1.70	0.41	4	0.67	0.73	109.0
Intra-assay (within-run) statistics (Pooled):								4.00	0.14	0.32	221.2
Inter-assay (between-run) statistics (ANOVA):								24	0.14	0.36	264.3
Low (1.92,000)	04-Jan-11	1	201101061602.008	3.44	3.46	3.11	2.67	4	3.22	0.28	8.6
	05-Jan-11	1	201101062334.008	^(b) 2.52	1.91	^(b) 1.37	2.43	4	2.06	0.53	25.8
	07-Jan-11	1	201101082013.008	2.87	2.59	2.58	3.68	4	2.93	0.52	17.7
	04-Jan-11	2	201101060157.008	2.16	2.12	2.54	2.54	4	2.34	0.23	9.9
	05-Jan-11	2	201101061917.008	3.44	3.37	3.30	2.26	4	3.09	0.56	16.0
	08-Jan-11	2	201101071831.008	2.12	2.63	2.26	2.55	4	2.39	0.24	10.0
Intra-assay (within-run) statistics (Pooled):								4.00	2.67	0.42	15.7
Inter-assay (between-run) statistics (ANOVA):								24	2.67	0.59	22.3

^(a) Re-prepared the minimum required dilution of this sample due to a possible error in the first preparation.

^(b) Cannot be calculated due to the denominator = 0.

Note: All negative control values fall below the cut point and sensitivity of the assay resulting in high imprecision.

	Assay Date	Analyst	Assay ID	%B/T				Intra-assay (within-run) Statistics			
				1st	2nd	3rd	4th	n	Mean	Std Dev	%CV
				Front	Front Mid	Back Mid	Back				
Mid (11.5,000)	04-Jan-11	1	201101061602.008	20.78	21.45	19.07	12.66	4	18.49	4.01	21.7
	05-Jan-11	1	201101062334.008	19.68	19.56	19.16	19.77	4	19.54	0.27	1.4
	07-Jan-11	1	201101082013.008	19.49	19.83	19.61	21.53	4	20.12	0.95	4.7
	04-Jan-11	2	201101060157.008	19.28	18.83	19.92	19.16	4	19.30	0.45	2.4
	05-Jan-11	2	201101061917.008	21.05	21.66	21.32	22.34	4	21.60	0.56	2.6
	08-Jan-11	2	201101071831.008	18.06	11.82	16.38	18.07	4	16.08	2.95	18.3
Intra-assay (within-run) statistics (Pooled):								4.00	19.19	2.09	10.9
Inter-assay (between-run) statistics (ANOVA):								24	19.19	2.58	13.5
High (11.2,000)	04-Jan-11	1	201101061602.008	50.39	46.51	49.02	46.70	4	48.66	1.53	3.1
	05-Jan-11	1	201101062334.008	47.83	46.91	47.46	48.95	4	47.79	0.66	1.8
	07-Jan-11	1	201101082013.008	45.42	46.60	44.76	^(c) 38.79	4	43.89	3.49	7.9
	04-Jan-11	2	201101060157.008	49.24	46.34	49.16	48.66	4	48.85	0.43	0.9
	05-Jan-11	2	201101061917.008	51.45	49.95	49.96	51.03	4	50.60	0.76	1.5
	08-Jan-11	2	201101071831.008	42.47	40.69	39.25	42.12	4	41.13	1.47	3.6
Intra-assay (within-run) statistics (Pooled):								4.00	46.82	1.74	3.7
Inter-assay (between-run) statistics (ANOVA):								24	46.82	3.87	8.3

^(c) Calculated from the mean of replicate results where one of the LY2963016 tubes had been split. Data included in summary statistics.

Note: Precision Data for Total LY2963016 was calculated using assay-specific reactivity cut point. Any result that was calculated to be a negative value was reported as 0.00 %B/T.

Reviewer's comment: The cumulative responses for positive samples demonstrated a variability ranging from 3.7 to 15.7 %CV for intra-assay and from 8.3 to 22.3 %CV for inter-assay statistics. The 22.3 %CV was due to one individual sample response for the low positive control and while it does not meet the 20% validation plan acceptance criteria, this result (1 of 6 samples) could be acceptable for a low level of anti-insulin antibodies sample. Additionally, 4 of the 24 negative control reading had %BT above the cut-point (0.26%BT) which is not very unusual for a negative control samples.

In this assay, the mean negative control was different than it was found in previous precision assay presented in Table 5. This may be possible because in this assay precision data for Total LY2963016 was calculated by subtracting %B/T of LY2963016 with excess unlabeled LY2963016 from %B/T LY2963016, thus the mean for the negative controls was different than previous precision assay. The precision for LY2963016 is acceptable.

9.1.3 Precision of Insulin Cross-Reactivity Response for Validation Samples:

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The Sponsor stated that 6 runs were processed for the assessment of intra- and inter-assay precision, with three determinations for each run of the three positive controls (Low, Mid and High) and negative control concentrations (n=18). The validation samples were prepared by spiking guinea pig polyclonal anti-insulin hyper-immune serum into pooled normal human serum at dilutions of 1:32,000, 1:5,500, and 1:2,000 to prepare low, mid and high positive controls respectively. The precision data are presented in Table 7.

Table 7 Precision of Insulin Cross-Reactivity Response for Validation Samples

	Assay Date	Analyst	Assay ID	%B/T				Intra-assay (within-run) Statistics			
				1st	2nd	3rd	4th	n	Mean	Std Dev	%CV
				Front	Front Mid	Back Mid	Back				
Negative	04-Jan-11	1	201101061602.008	1.16	0.35	0.00	0.46	4	0.50	0.49	97.7
	05-Jan-11	1	201101062334.008	0.60	0.51	0.00	0.21	4	0.18	0.24	134.0
	07-Jan-11	1	201101062013.008	0.56	2.02	0.73	0.91	4	1.06	0.66	62.5
	04-Jan-11	2	201101060157.008	0.53	0.00	0.00	0.83	4	0.34	0.41	121.0
	05-Jan-11	2	201101061917.008	0.59	0.79	0.72	0.68	4	0.70	0.08	12.0
	06-Jan-11	2	201101071831.008	0.00	1.15	2.11	1.13	4	1.10	0.86	78.6
	Intra-assay (within-run) statistics (Pooled):							4.00	0.64	0.52	81.4
	Inter-assay (between-run) statistics (ANOVA):							24	0.64	0.59	91.5
Low (1:32,000)	04-Jan-11	1	201101061602.008	3.70	3.84	3.88	3.66	4	3.77	0.11	2.8
	05-Jan-11	1	201101062334.008	3.68	3.69	2.97	4.26	4	3.65	0.53	14.5
	07-Jan-11	1	201101062013.008	4.01	3.79	3.61	4.07	4	3.87	0.21	5.5
	04-Jan-11	2	201101060157.008	3.77	3.30	3.72	3.70	4	3.62	0.22	6.0
	05-Jan-11	2	201101061917.008	4.52	4.58	4.38	3.63	4	4.28	0.44	10.3
	06-Jan-11	2	201101071831.008	3.15	3.38	3.24	3.41	4	3.30	0.12	3.7
	Intra-assay (within-run) statistics (Pooled):							4.00	3.75	0.31	8.4
	Inter-assay (between-run) statistics (ANOVA):							24	3.75	0.42	11.3
Mid (1:5,500)	04-Jan-11	1	201101061602.008	21.07	22.30	19.97	12.28	4	18.91	4.52	23.9
	05-Jan-11	1	201101062334.008	20.71	21.93	20.54	21.25	4	21.11	0.63	3.0
	07-Jan-11	1	201101062013.008	20.42	21.02	20.40	22.81	4	21.16	1.14	5.4
	04-Jan-11	2	201101060157.008	20.26	19.91	20.80	19.93	4	20.23	0.42	2.1
	05-Jan-11	2	201101061917.008	22.40	23.06	22.22	23.01	4	22.67	0.43	1.9
	06-Jan-11	2	201101071831.008	18.90	12.61	17.31	19.14	4	16.99	3.03	17.8
	Intra-assay (within-run) statistics (Pooled):							4.00	20.18	2.30	11.4
	Inter-assay (between-run) statistics (ANOVA):							24	20.18	2.81	14.0
High (1:2,000)	04-Jan-11	1	201101061602.008	50.83	49.44	49.51	47.48	4	49.32	1.38	2.8
	05-Jan-11	1	201101062334.008	50.30	48.76	49.44	50.43	4	49.73	0.78	1.6
	07-Jan-11	1	201101062013.008	48.36	47.41	45.98	^{1a} 39.45	4	44.80	3.62	8.1
	04-Jan-11	2	201101060157.008	50.21	49.82	49.95	50.27	4	50.06	0.21	0.4
	05-Jan-11	2	201101061917.008	53.04	51.27	50.97	52.36	4	51.91	0.96	1.9
	06-Jan-11	2	201101071831.008	43.98	41.39	40.36	43.05	4	42.20	1.63	3.9
	Intra-assay (within-run) statistics (Pooled):							4.00	48.00	1.79	3.7
	Inter-assay (between-run) statistics (ANOVA):							24	48.00	4.01	8.3

^{1a} Calculated from the mean of replicate results where one of the LY2963016 tubes had been spilled. Data included in summary statistics.

Note: Precision Data for Insulin cross-reactivity was calculated using assay-specific reactivity. Any result that was calculated to be a negative value was reported as 0.00 %B/T.

Reviewer's comment: The cumulative responses for all positive samples were in increase in order from NC to high controls with variability ranging from 3.7 to 11.4 %CV for intra-assay and from 8.3 to 14.0 %CV for inter-assay statistics. The negative controls had very high CV%, however all data were below the cut-point for the assay (1.06%BT). Precision Data for Cross-reactive to Insulin was calculated by subtracting %B/T with excess Insulin from %B/T LY2963016, thus the mean for the negative controls was different than it was found in previous precision assay presented in Table5 and Table6. The precision for LY2963016 is acceptable.

9.2 Matrix Selectivity (spike and recovery):

For matrix selectivity assay, the Sponsor stated, ten (10) different lots of serum from normal healthy adults were spiked with the antibody at the NC, Low, Mid and High concentrations or dilution (N=1). These values were compared to a base pool (10 lots), that was used as reference. The data are presented in **Table 3**.

Table 3 Recovery of anti-LY2963016 in Human Serum (continued)

Lot Number	Assay Date	Analyst	Assay Number	Level of Positive GP Antisera in Normal Human Serum			
				Negative	^(a) Low	^(b) Mid	^(c) High
BRH419147M	15-Dec-10	1	201012161859.008	3.70	5.90	21.95	54.61
Mean				3.70	5.90	21.95	54.61
% Recovery of NHS Serum Pool Response					89.17	87.59	102.21
BRH419148M	15-Dec-10	1	201012161859.008	3.36	6.44	24.72	55.64
Mean				3.36	6.44	24.72	55.64
% Recovery of NHS Serum Pool Response					97.35	98.65	104.14
BRH419149M	15-Dec-10	1	201012161859.008	2.93	6.71	26.19	55.91
Mean				2.93	6.71	26.19	55.91
% Recovery of NHS Serum Pool Response					101.31	104.52	104.65
BRH419150M	15-Dec-10	1	201012161859.008	4.15	7.53	25.10	54.75
Mean				4.15	7.53	25.10	54.75
% Recovery of NHS Serum Pool Response					113.70	100.16	102.48
BRH419151M	15-Dec-10	1	201012161859.008	3.20	6.89	25.69	54.46
Mean				3.20	6.89	25.69	54.46
% Recovery of NHS Serum Pool Response					104.03	102.53	101.93
n				30			
n of passing samples				30			
% of passing samples				100.0			

^(a) "Low" concentrations were prepared using a 1:32,000 dilution of antisera in matrix.

^(b) "Mid" concentrations were prepared using a 1:5,500 dilution of antisera in matrix.

^(c) "High" concentrations were prepared using a 1:2,000 dilution of antisera in matrix.

Reviewer's Comment: *The Sponsor used high, low and medium PC controls to demonstrate the selectivity of the sample. In general, the selectivity is performed to assess the ability of the assay to measure the analyte of interest in presence of other sample constituent in order to understand if any component in the sample prevents the assay from detecting the antibody. It is characterized by the recovery of analyte from the matrix sample. The data from this assay showed that % recovery of all samples were good between 87-113% demonstrating the selectivity of the product.*

9.3 Sensitivity:

The Sponsor stated that a titration of the affinity purified guinea pig anti-Insulin antibody were prepared at concentrations of 2000, 1000, 500, 250, 125, 62.5, 31.3, 15.6, 7.8 & 0 ng/ml in pooled human serum. Sensitivity was performed in two (2) runs by one analyst in 2 days and was assessed using the value calculated for cut point plotted against a sensitivity curve. The data are shown in **Table 8** and graphically in **Figure 1**.

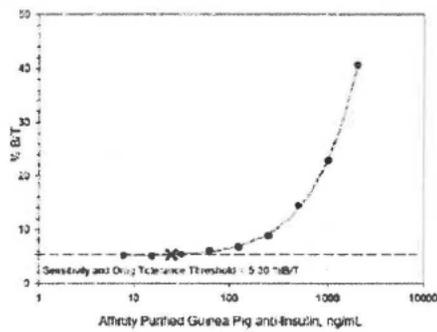
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Table 8 Sensitivity

Assay Date	Analyst	Assay ID	%B/T									
			Concentration of Affinity Purified Guinea Pig Anti-Insulin (ng/mL)									
			0.0	7.8	15.6	31.3	62.5	125.0	250.0	500.0	1000.0	2000.0
21-Dec-10	1	201012230912.008	4.29	5.15	5.09	5.39	6.02	6.75	8.87	14.50	22.91	40.66
22-Dec-10	1	201012231357.008	5.33	5.57	5.06	5.36	6.81	7.89	9.99	15.11	23.87	41.30
Mean			4.81	5.36	5.07	5.39	6.41	7.32	9.43	14.80	23.39	40.98
n			2	2	2	2	2	2	2	2	2	2
Standard Deviation			0.73	0.39	0.02	0.01	0.56	0.80	0.79	0.44	0.68	0.45
Precision (%CV)			15.2	5.5	0.4	0.1	8.7	11.0	8.4	2.9	2.9	1.1

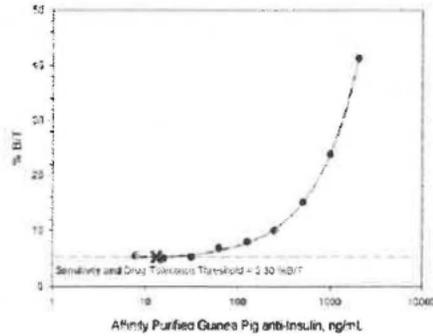
Note: Sensitivity was calculated using the assay screening sensitivity and drug tolerance threshold value of 5.30 %B/T.

Figure 1 Sensitivity
Figure 1A.



Assay 1:
Using the screening cut-point of 5.30 %B/T and interpolating in StatLIA yields a sensitivity of 25.0 ng/mL anti-insulin.

Figure 1B.



Assay 2:
Using the screening cut-point of 5.30 %B/T and interpolating in StatLIA yields a sensitivity of 13.2 ng/mL anti-insulin.

Reviewer's comment: The Sponsor calculated the assay screening cut-point and drug tolerance threshold value from two assays as an unknown and interpolated from the sensitivity curve using a 5-parameter logistical curve fit. Using affinity purified polyclonal anti-insulin antibody, the sensitivity was determined to be 25ng/mL for assay 1 and 13.2ng/mL for assay 2. The sensitivity was reported as the more conservative value of 25ng/mL which is good and accepted.

9.4 Drug Tolerance:

Drug tolerance: The Sponsor used 500ng/ml of the affinity purified guinea pig anti-Insulin that was subjected to levels of 250, 1250 & 2500 ng/ml LY2963016 in two runs. The level of drug necessary to drop the response below the cut point was determined. The data are shown in **Table 9** and graphically in **Figure 2**.

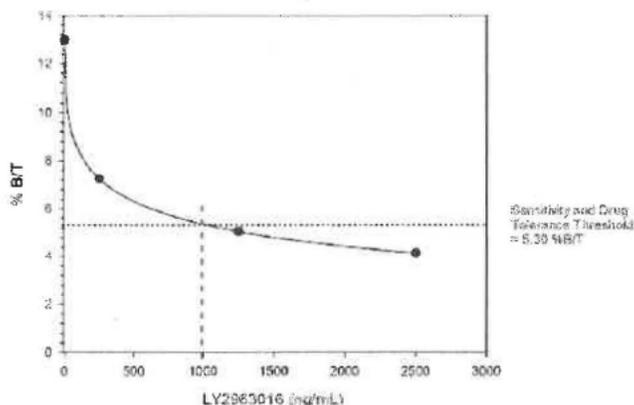
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Table 9 LY2963016 Tolerance

Affinity Purified Guinea Pig Anti-Insulin	Assay Date	Analyst	Assay Number	%B/T			
				Concentration of LY2963016 (ng/mL)			
				0	250.0	1250.0	2500.0
500 ng/mL	28-Dec-10	2	201012291407.008	12.89	7.02	4.93	4.18
	28-Dec-10	2	201012291545.008	13.10	7.36	5.01	3.68
				13.43	7.40	4.80	4.18
				12.48	7.21	5.41	4.44
				12.98	7.25	5.04	4.12
				0.40	0.17	0.26	0.32
				3.1	2.4	5.2	7.7
					44.14	61.18	68.25

Note: LY2963016 Tolerance was calculated using the assay screening sensitivity and drug tolerance threshold value of 5.30 %B/T. The mean of assay results for assays 201012291407.008 and 201012291545.008 were plotted against increasing concentrations of LY2963016 (screening sensitivity and drug tolerance threshold = 5.30 %B/T). At 500 ng/mL of affinity purified polyclonal anti-insulin antibody, concentrations of up to 250 ng/mL LY2963016 do not drop the response to below the screening sensitivity and drug tolerance threshold. The data are shown graphically in Figure 2.

Figure 2 LY2963016 Tolerance Graph



Reviewer's comment: The Sponsor stated that they ran two assays (201012291407.008 and 201012291545.008) and mean of assay results were plotted against increasing concentrations of LY2963016 (assay cut-point = 5.30 %B/T). The tolerance graph demonstrated that at 500 ng/mL of affinity purified polyclonal anti-insulin antibody, concentrations of up to 1000ng/mL LY2963016 did not drop the response to below the assay screening threshold. This assay method can tolerate the drug, LY2963016 concentrations up to 1000ng/mL without decreasing the signal to at or below the assay cut-point in presence of 500ng/mL anti-LY2963016 antibody.

Insulin tolerance: The Sponsor stated that 500 ng/ml of the Affinity purified guinea pig anti-Insulin was subjected to levels of 250, 1250 & 2,500 ng/ml Insulin in two runs. The level of drug necessary to drop the response below the cut point was determined. The data are shown in Table 10 and graphically in Figure 3.

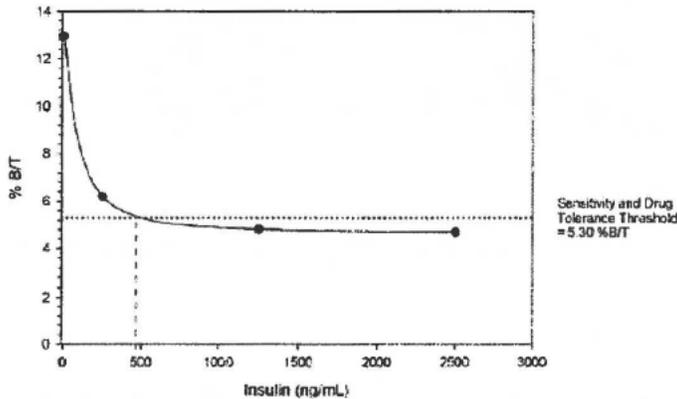
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Table 10 Insulin Tolerance

				%B/T			
				Concentration of Insulin (ng/mL)			
Affinity Purified Guinea Pig Anti-Insulin	Assay Date	Analyst	Assay Number	0.0	250.0	1250.0	2500.0
500 ng/mL	28-Dec-10	2	201012291407.008	12.89	6.07	4.86	4.42
				13.10	6.56	4.69	4.61
	28-Dec-10	2	201012291545.008	13.43	6.00	4.45	4.75
				12.48	6.17	5.29	5.02
Mean				12.98	6.20	4.82	4.70
Standard Deviation				0.40	0.25	0.35	0.25
Precision (%CV)				3.1	4.0	7.3	5.4
% Inhibition Relative to 0					52.22	62.63	63.78

Note: Insulin tolerance was calculated using the assay screening sensitivity and drug tolerance threshold value of 5.30 %B/T. The mean of assay results for assays 201012291407.008 and 201012291545.008 were plotted against increasing concentrations of insulin (screening sensitivity and drug tolerance threshold = 5.30 %B/T). At 500 ng/mL of affinity purified anti-insulin antibody, concentrations of up to 250 ng/mL of insulin do not drop the response to below the screening sensitivity and drug tolerance threshold. The data are shown graphically in Figure 3.

Figure 3 Insulin Tolerance Graph



Reviewer's comment: The Sponsor stated that they ran two assays (201012291407.008 and 201012291545.008) and mean of assay results were plotted against increasing concentrations of LY2963016 (assay cut-point = 5.30 %B/T). The tolerance graph demonstrated that at 500 ng/mL of affinity purified polyclonal anti-insulin antibody, concentrations of up to 500ng/mL LY2963016 did not drop the response to below the assay screening threshold. This assay method can tolerate insulin concentrations up to 500ng/mL without decreasing the signal to at or below the assay cut-point in presence of 500ng/mL anti-LY2963016 antibody.

9.5 Stability during Sample Processing:

9.5.1 Room and Refrigerated Temperature Stabilities:

The Sponsor stated that three aliquots of the NC, Low, Mid and High validation samples were placed at 2-8°C and room temperature for 4 hours prior to analysis. Three aliquots of the NC, Low, Mid and High validation samples thawed at the time of the assay (Reference). Three determinations for each concentration were analyzed.

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Table 11 Room and Refrigerated Temperature Stabilities

Reference			%B/T			
Assay Date	Analyst	Assay Number	Negative	Low (1:32,000)	Mid (1:5,500)	High (1:2,000)
28-Dec-10	2	201012291750.008	4.43	7.24	24.79	52.27
			4.70	7.59	24.67	54.14
			4.30	7.75	26.05	53.59
Mean			4.48	7.53	25.17	53.34
Standard Deviation			0.20	0.26	0.76	0.98
Precision (%CV)			4.5	3.4	3.0	1.8

Stability After 4 Hours			Stability at 2 to 8 °C				Stability at Ambient Temperature (15 to 30 °C)			
Assay Date	Analyst	Assay Number	Negative	Low (1:32,000)	Mid (1:5,500)	High (1:2,000)	Negative	Low (1:32,000)	Mid (1:5,500)	High (1:2,000)
28-Dec-10	2	201012291750.008	3.63	7.46	24.83	52.84	3.64	6.69	24.48	53.23
			4.21	7.79	23.77	54.57	6.70	7.62	23.87	52.84
			3.81	7.85	24.43	51.22	4.12	7.52	25.03	58.97
Mean			3.88	7.70	24.35	52.88	4.82	7.27	24.46	55.05
Standard Deviation			0.30	0.21	0.53	1.87	1.65	0.51	0.58	3.44
Precision (%CV)			7.7	2.7	2.2	3.2	34.2	7.0	2.4	6.3
% Difference from Reference			-13.2	2.3	-3.3	-0.9	7.7	-3.4	-2.8	3.1

Stability After 24 Hours			Stability at 2 to 8 °C				Stability at Ambient Temperature (15 to 30 °C)			
Assay Date	Analyst	Assay Number	Negative	Low (1:32,000)	Mid (1:5,500)	High (1:2,000)	Negative	Low (1:32,000)	Mid (1:5,500)	High (1:2,000)
28-Dec-10	2	201012291750.008	4.22	7.41	23.80	52.08	3.30	6.81	25.17	55.11
			4.30	7.98	24.06	55.94	3.63	6.94	26.20	55.40
			4.27	7.96	25.67	57.14	3.61	7.90	25.29	55.67
Mean			4.26	7.78	24.51	55.05	3.51	7.21	25.55	55.39
Standard Deviation			0.04	0.32	1.01	2.65	0.18	0.59	0.57	0.23
Precision (%CV)			0.9	4.1	4.1	4.8	5.2	8.2	2.2	0.5
% Difference from Reference			-4.8	3.4	-2.6	3.2	-21.5	-4.2	1.5	3.9

Reviewer's comment: The assay variability (CV%) looks good. The data demonstrated the stability of the product for up to 24 hours at room temperature and at refrigerated temperature (2 – 8 °C).

9.5.2 Freeze-Thaw Stability:

The Sponsor stated that three aliquots of the NC, Low, Mid and High validation samples were subjected to a minimum of 8 freeze and thaw cycles. The stability validation samples were stored at the intended temperature for at least 24 hours and then thawed at room temperature up to 8 cycles. Three determinations for each concentration were analyzed.

Table 12 Freeze-Thaw Stability

Reference 1X			%B/T			
Assay Date	Analyst	Assay Number	Negative	Low (1:32,000)	Mid (1:5,500)	High (1:2,000)
06-Jan-11	1	201101072117.008	3.46	6.76	^(a) 15.79	^(b) 7.75
			3.85	6.80	23.29	^(c) 34.12
			3.59	6.30	22.46	49.62
Mean			3.64	6.62	22.88	49.62
Standard Deviation			0.20	0.28	0.58	^(c) —
Precision (%CV)			5.5	4.2	2.6	^(c) —

Freeze-Thaw 2X			%B/T			
Assay Date	Analyst	Assay Number	Negative	Low (1:32,000)	Mid (1:5,500)	High (1:2,000)
06-Jan-11	1	201101072117.008	3.84	6.74	22.54	50.07
			4.22	7.28	^(a) 17.89	^(b) 40.56
			4.24	6.83	^(b) 18.90	50.71
Mean			4.10	6.95	22.54	50.39
Standard Deviation			0.22	0.29	^(c) —	0.45
Precision (%CV)			5.5	4.2	^(c) —	0.9
% Difference from Reference			12.9	4.9	-1.5	1.8

Insulin Glargine-NDA205692

Freeze-Thaw 6X

06-Jan-11	1	201101072117.008
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^{ib} 7.05	7.45	22.69	52.70
4.15	6.99	23.13	50.03
4.28	6.83	22.94	50.76

Mean
Standard Deviation
Precision (%CV)
% Difference from Reference

4.21	7.09	22.92	51.16
0.09	0.32	0.22	1.38
2.2	4.5	1.0	2.7
15.8	7.2	0.2	3.1

Freeze-Thaw 8X

06-Jan-11	1	201101072117.008
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4.00	6.23	22.87	48.40
4.34	6.56	22.51	46.78
3.95	6.74	22.32	47.07

Mean
Standard Deviation
Precision (%CV)
% Difference from Reference

4.10	6.51	22.57	47.42
0.21	0.26	0.28	0.86
5.2	4.0	1.2	1.8
12.7	-1.6	-1.4	-4.4

Reviewer's comment: *The assay variability looks good. The data demonstrated the stability of the product for up to 24 hours at room temperature and at refrigerated temperature (2 – 8 °C).*

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

/s/

FARUK G SHEIKH
02/04/2014

DANIELA I VERTHELYI
02/04/2014

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		
NDA # 205692	NDA Supplement #:S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: TBD Established/Proper Name: insulin glargine (rDNA origin) Dosage Form: injection Strengths: 100 units/mL		
Applicant: Eli Lilly and Company Agent for Applicant (if applicable): N/A		
Date of Application: 10/17/2013 Date of Receipt: 10/18/2013 Date clock started after UN: N/A		
PDUFA Goal Date: 8/18/2014	Action Goal Date (if different): 8/18/2014	
Filing Date: 12/17/2013	Date of Filing Meeting: 12/4/2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Improve glycemic control in Type 1 (adults and children) and Type 2 (adults) diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <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: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
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>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <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 checked="" 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 checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input 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(s): 105423				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><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></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><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></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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)].</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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)]?</p> <p><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></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input checked="" type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><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></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<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>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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>				
Debarment Certification	YES	NO	NA	Comment
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&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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</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 & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If studies or full waiver not included , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	PNR submitted under IND 105423 on 5/13/13
REMS	YES	NO	NA	Comment
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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input 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)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH and DMPP consulted 10/22/13

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 8/28/13	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 4, 2013

BLA/NDA/Supp #: 205692

PROPRIETARY NAME: (b) (4) KwikPen

ESTABLISHED/PROPER NAME: insulin glargine (rDNA origin)

DOSAGE FORM/STRENGTH: 100 unit/mL injection

APPLICANT: Eli Lilly and Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Improve glycemic control in Type 1 (adults and children) and Type 2 (adults) diabetes mellitus

BACKGROUND: Insulin glargine is a long acting insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes and adults with type 2 diabetes. Lantus was approved under NDA 21081 on April 20, 2000. On October 18, 2013 Eli Lilly submitted a 505(b)(2) application to rely on the FDA finding of safety and effectiveness for Lantus. Eli Lilly has provided a bridge to both US approved Lantus as well as EU approved Lantus and has also submitted Phase 3 studies.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Callie Cappel-Lynch	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Ali Mohamadi		Y
Clinical	Reviewer:	Lisa Yanoff	Y
	TL:	Ali Mohamadi	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Manoj Khurana	Y
	TL:	Lokesh Jain	Y
Biostatistics	Reviewer:	Lee Ping Pian	Y
	TL:	Mark Rothmann	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai-Turton	Y
	TL:	Karen Davis-Bruno	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Faruk Sheik	Y
	TL:	Daniela Verthelyi	N
Product Quality (CMC)	Reviewer:	Ysern Xaveier Muthukumar Ramaswamy	Y
	TL:	Suong Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	N
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Cynthia Kleppinger	Y
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	Sarah Vee	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Human Factors	Quynh Nguyen /TL Ron Kaye		N/N
Combination Products	Patricia Beaston and Lening Shen/ TLKeith Marin		Y/N
Other attendees			
Office of Prescription Drug Promotion	Ankur Kalola		
Division of Medical Policy Programs	Shawna Hutchins		
Office of Regulatory Policy	Janice Weiner		
Division of Pharmacovigilance	Christine Chamberline		
Office of Combination Products	Patricia Love		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO The bridge for this application consists of a BA/BE study between US approved Lantus and the test product as well as a BA/BE study between EU approved Lantus and the test product. A BA/BE study was also performed between US and EU approved Lantus.
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: no comments</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: Not anticipated at this time</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"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: N/A
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments: N/A</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> 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? <p>Comments: N/A</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments: N/A</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable

<p>Comments: None</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: N/A</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Comments: Need filter validation studies</p>	
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: N/A</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments: N/A</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: N/A</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • 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? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): March 17, 2014

21st Century Review Milestones (see attached)

- a. Receipt date: October 18, 2013
- b. Filing Date: December 17, 2013
- c. 74-Day letter must issue on December 31, 2013
- d. Mid-Cycle Review meeting: March 17, 2014
- e. Primary Reviews due: July 14, 2014
- f. Wrap-Up Meeting: July 14, 2014 (tentative)
- g. Secondary Reviews due: July 21, 2014
- h. Send proposed labeling/PMR/PMC to sponsor: July 28, 2014
- i. CDTL Review due: July 28, 2014
- j. Action package to Division Director: July 28, 2014
- i. Sign Action letter: August 18, 2014 (PDUFA goal date)

Comments: N/A

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p>

<input type="checkbox"/>	Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	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
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • 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) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	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: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	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.

/s/

CALLIE C CAPPEL-LYNCH
12/11/2013

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: [NDA 205692](#)

Application Type: New NDA

Name of Drug: (b)(4) KwikPen (insulin glargine [rDNA origin] injection)

Applicant: Eli Lilly and Company

Submission Date: October 17, 2013

Receipt Date: October 18, 2013

1.0 Regulatory History and Applicant's Main Proposals

This application provides for an insulin glargine pre-filled pen device indicated to improve glycemic control in adults and children with Type 1 diabetes and adults with Type 2 diabetes. This is a 505(b)(2) application which relies on the FDA finding of safety and efficacy for Lantus. Lantus was approved under NDA 21081 on April 20, 2000. A pre- NDA meeting was held on August 28, 2013.

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).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74 Day Letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 21, 2014. The resubmitted PI will be used for further labeling review.

4.0 Appendix

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.

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:

- NO** 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).

Selected Requirements of Prescribing Information (SRPI)

Comment:

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	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

NO

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: *Remove space before paragraph*

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:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- N/A** 12. All text must be **bolded**.
Comment:
- N/A** 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:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- N/A** 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:
- N/A** 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:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- 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:

- N/A** 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:

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:

YES

Selected Requirements of Prescribing Information (SRPI)

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:

- N/A** 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:

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.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 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:

- N/A** 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

- N/A** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

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: *Clinical team leader verified that the modification used is acceptable and appropriate.*

- YES** 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

- NO** 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: All pieces of labeling are not referenced.

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/s/

CALLIE C CAPPEL-LYNCH
12/09/2013

Date: December 5, 2013
From: Lening Shen, WO66, RM 2558
General Hospital Devices Branch, DAGRID, ODE, CDRH
To: Callie Cappel-Lynch, DMEP/CDER
Subject: CDRH Consult, ICC1300540, NDA 205692, Eli Lilly and Company
LY2963016 KwikPen™ (LY2963016 KP)
Consultants: Patricia Beaston, MD, Ph.D, Clinician, CDRH/ODE/DAGRID

1. Issue

This consult is to determine if the sponsor has provided enough device related information for CDRH to conduct a 510(k) clearance type of review on the device of the submission.

2. Documents Reviewed

Section 3.2.R.3 (medical-device.pdf)

3. CDRH Review and Comments

Based on the information provided above, I believe that the sponsor did not provide enough information for us to conduct a full review of the device. Mainly, the sponsor only provided tables list all test conducted and test results, no test reports with details were provided for us to review. Additionally, it appears that the biocompatibility testing is conducted on the resins rather than on the final and finished product as we require. Sterility information is not present.

Dr. Patricia Beaston reviewed the summary data and concluded that the sponsor has submitted adequate information for her to conduct a clinical review of the device component. However, this summary data must be supported by the information requested below.

4. CDRH Recommendation

CDRH/ODE recommends obtaining the following device information from the NDA sponsor:

1. All detailed test reports for tests conducted based on ISO 11608. Including test protocol, test data, pass/fail criteria and test results.
2. Biocompatibility test reports on the final and finished product. The sponsor has submitted the MSDS for the device component resin. However, we require biocompatibility tests results based on the final and finished product.

3. Sterility report. We did not locate any information on this issue.

Digital Signature Concurrence Table	
Reviewer Sign-Off	<p>Lening Shen -S</p> <p>Digitally signed by Lening Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lening Shen -S, 0.9.2342.19200300.100.1.1=1300435455 Date: 2013.12.05 09:56:11 -05'00'</p>
Branch Chief Sign-Off	<p>Kathleen E. Fitzgerald</p> <p>Digitally signed by Kathleen E. Fitzgerald DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093027, cn=Kathleen E. Fitzgerald Date: 2013.12.05 10:04:00 -05'00'</p>

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/s/

CALLIE C CAPPEL-LYNCH
12/05/2013
consult review for Lening Shen